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Data-driven discoveries on widespread contamination of freshwater reservoirs by dominant antibiotic resistance genes

Zhao-Feng Guo [a,b,c], Wiebke J. Boeing [d], Yao-Yang Xu [a,c,*], Edoardo Borgomeo [e], Dong Liu [a,b,c], Yong-Guan Zhu [a,c]

[a] *Key Laboratory of Urban Environment and Health, Ningbo Observation and Research Station, Institute of Urban Environment, Chinese Academy of Sciences, Xiamen 361021, PR China*
[b] *University of Chinese Academy of Sciences, Beijing 100049, PR China*
[c] *Zhejiang Key Laboratory of Urban Environmental Processes and Pollution Control, CAS Haixi Industrial Technology Innovation Center in Beilun, Ningbo 315830, PR China*
[d] *Department of Fish, Wildlife & Conservation Ecology, New Mexico State University, Las Cruces, NM 88003, USA*
[e] *Environmental Change Institute, University of Oxford, Oxford OX1 3QY, UK*

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ABSTRACT

The propagation of antibiotic resistance genes (ARGs) in freshwater reservoirs threatens ecosystem security and human health, and has attracted increasing attention. A series of recent research articles on ARGs provides a unique opportunity for data-driven discoveries in this emerging field. Here, we mined data from a total of 290 samples from 60 reservoirs worldwide with a data-driven framework (DD) developed to discover geographical distribution, influencing factors and pollution hotspots of ARGs in freshwater reservoirs. Most data came from Asia and Europe where nine classes of ARGs were most frequently detected in reservoirs with multi-drug resistance and sulfonamide resistance genes prevailing. Factors driving distribution of reservoir ARGs differed between reservoir waters and sediments, and interactions among these factors had linear or nonlinear enhancement effects on the explanatory power of ARG distribution. During the cold season, small-sized reservoir waters rich in organic carbon, mobile genetic elements (MGEs) and antibiotics had a higher pollution potential of ARGs; during the spring drought, sediments in large reservoirs located in densely populated areas were more conducive to dissemination of ARGs due to their richness in antibiotics and MGEs. Thus, distribution pattern of ARG pollution hotspots in reservoir waters and sediments varies greatly depending on the differences of internal and external factors. From the "One Health" perspective, this widespread contamination of freshwater reservoirs by ARGs we discovered through the DD framework should be a push to promote integrated research across regions and disciplines. Especially the human - food-chain - ecosystem interface needs an improved understanding of ARG contamination mechanisms and targeted monitoring and evaluation systems should be developed to maintain all ecosystem services in freshwater reservoirs as well as to safeguard human health.

1. Introduction

Dissemination of antibiotic resistance genes (ARGs) across species and regions has caused antibiotic resistance to become globalized, posing a serious threat to public health and food safety. Antibiotics reach aquatic ecosystems through sewage discharge, surface runoff, and aquaculture, contributing to the rise and proliferation of ARGs within antibiotic-resistant bacteria (Hendriksen et al., 2019; Schar et al., 2021). With an increase in human activities, exposure of aquatic ecosystems to ARGs usually increases (Zhu et al., 2017). As the "One Health" approach emphasizes, ARG pollution endangers health and wellbeing of humans, animals, and the environment, and accelerated globalization is driving the transfer among those three (Chatterjee et al., 2018; Vikesland et al., 2017). Given that the occurrence of ARGs and antibiotic resistance may increase virulence, pathogenicity, and mortality (Berendonk et al., 2015), the World Health Organization (WHO) views their global dissemination as a crisis that threatens global public health security and the core of modern medicine (WHO, 2015).

Reservoirs, artificial freshwater storage systems constructed by damming to secure water needs, have potential to become important

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* Corresponding author at: Institute of Urban Environment Chinese Academy of Sciences, Jimei Road 1799, Jimei District, Xiamen, China.
E-mail address: yyxu@iue.ac.cn (Y.-Y. Xu).

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dissemination channels for ARGs from environment to humans. Bacterial communities in waters can perpetuate ARGs originating from sewage (Marti et al., 2014; Rodriguez-Mozaz et al., 2015). Even advanced water treatment technologies have difficulty in completely removing ARGs and limiting their occurrence and abundance (Garner et al., 2018). Reservoirs usually receive both rain/river and wastewater for drinking water storage, facilitating ARGs transfer from environment to aquatic organisms and humans (Martínez, 2008). ARGs could eventually contribute to emergence of antibiotic resistance in humans through food chain or direct contact, thus enabling cross-species gene sharing (Pehrsson et al., 2016; Van Boeckel et al., 2015). Thus, freshwater reservoirs play an important role in the propagation of ARGs, and controlling their increase of resistance can help reduce human mortality rate and medical burden to some extent.

Given the potential threat of ARGs to multiple ecosystem services in reservoirs, research on occurrence and mechanisms driving the spread of ARGs is crucial to ensure water security and health. Faced with the current situation of widespread ARG contamination, researchers have paid increasing attention to what factors mainly influence the distribution of ARGs. Because antibiotics exert persistent selection pressure on microorganisms, an association between antibiotic residues and antibiotic resistance has been discovered in reservoirs (Chen et al., 2019). Several biotic and abiotic factors such as presence of bacterial communities, metals (e.g., Cu and Zn), mobile genetic elements (MGEs), and seasonal variation are considered to be key influencing factors of ARGs variability in reservoirs as well as directly interact with ARGs to some extent (Bengtsson-Palme et al., 2018; Laffite et al., 2020).

While exploring distribution and factors influencing ARGs in individual reservoirs has clear benefits for water safety management of the reservoir itself, a comprehensive scientific understanding of issue on a large-scale perspective regarding ARGs is yet to be developed. On one hand, reservoirs are frequently disturbed by anthropogenic activities making external drivers of ARGs diverse and complex; on the other hand, it is unclear how internal factors such as storage capacity, reservoir level, and reservoir catchment area affect how ARGs respond to external driving forces. Therefore, to uncover the mechanisms impacting ARGs in a global context, suitable statistical tools are needed to effectively identify factors driving the distribution of ARGs in reservoirs in general and assess their importance.

In today’s information and data era, a rapidly growing number of studies focusing their research on ARGs in reservoirs presents a unique opportunity to integrate those data, gain generalized insights into ARG distribution, and identify research gaps. In order to elevate our understanding of the underlying mechanisms influencing distribution of ARG pollutants, we integrated published data to construct a data-driven framework (DD). The framework is a data-intensive scientific discovery-oriented approach that integrates multidimensional raw data collected through data extraction – data grouping – multivariate

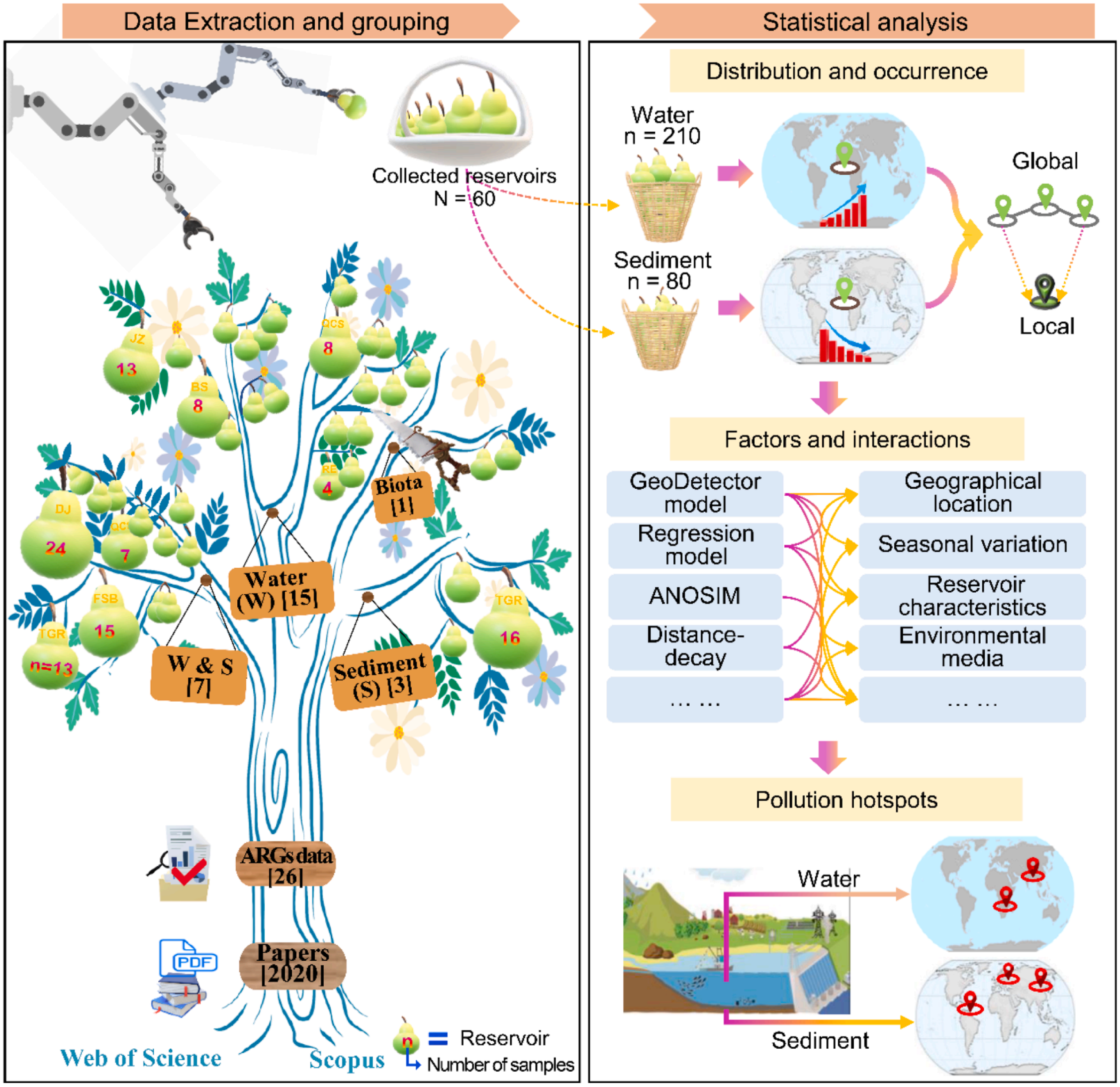

Fig. 1. Data-driven framework (DD). (a) data extraction and grouping; (b) statistical analysis.

statistics to determine current status of reservoir ARG pollution, identify problems with existing studies, and provide guiding recommendations for management of reservoir ARG pollution. DD framework was applied to address three questions: (i) global occurrence and distribution of ARGs in reservoirs; (ii) factors driving the distribution of ARGs in reservoirs and their interactions; and (iii) pollution hotspots, or potentially contaminated areas of ARGs in reservoirs. Based on the application of our DD framework, we gained important new insights into mechanisms impacting ARGs in reservoirs and their pollution hotspots. In our study we are highlighting key issues and challenges surrounding research of ARG pollution.

2. Data-driven framework

To investigate distribution and influencing mechanisms of ARGs in reservoirs, we constructed and applied a data-driven framework (DD) for data extraction and grouping as well as a statistical analysis (Fig. 1). First, we retrieved literature, screened publications according to inclusion criteria and extracted data from them. Acquired data were then grouped and analyzed using statistical methods to integrate results of existing studies. Our analyses and interpretations provide an intercontinental-scale perspective on the pollution profile of ARGs in reservoirs. Due to limited availability of data, this research is a preliminary basis for follow-up studies and analyses to further refine and adjust our findings.

2.1. Data extraction and grouping

To obtain data on reservoir ARGs, we conducted a search of the Web of Science and Scopus Database in December 2021 using the following subject terms: Topic = (“reservoir” OR “dam”) AND (“antibiotic* resistance gene*” OR “antibiotic* resistance bacteria” OR “antibiotic-resistant bacteria” OR “antimicrobial resistance” OR “antibiotic resistome”). The scope of the subject search included the title, abstract, and keyword list. Inclusion criteria consisted of research articles published in English, and a total of 2020 articles were retrieved. Among these articles, we selected the ones that measured abundance of ARGs in reservoirs. Since we were interested in variability of geographical distribution of ARG abundance, we contacted authors and requested additional data for studies that only provided averages of ARG abundance for multiple reservoirs or did not explicitly provide information on sample area. If the relevant information was still not available, we excluded those studies. Based on these screening criteria, 26 peer-reviewed papers published between 2010 and 2021 met the requirements. These 26 studies primarily investigated ARGs in reservoirs and sediments (25 articles), while only 1 article was conducted on organisms such as fish (Fig. 1a). Thus, 25 studies reporting ARGs in reservoir waters and sediments were found to provide comparable data and ultimately considered.

From the 25 eligible studies we extracted (i) sampling information such as sampling time and sampling site coordinates; (ii) reservoir characteristics including reservoir level, storage capacity, reservoir catchment area, and hydraulic residence time; (iii) data for ARGs, mobile genetic elements (MGEs), and antibiotic concentrations as well as common physicochemical parameters; and (iv) quantifying methods of ARGs. The range of data collection included text, tables, and figures. Where raw data were presented in the form of graphs, data were extracted using GetData Graph Digitizer V2.26 (error analysis of data extraction; see Text S1). Abundance of ARGs from the same sampling site at different sampling times was considered a different data point. Units of ARG abundance were expressed as copies/16S rRNA (relative abundance: gene copy number of ARGs was divided by 16S rRNA) or copies/mL (absolute abundance). In study that provided absolute abundance of ARGs in reservoirs, two main quantitative methods, high-throughput quantitative polymerase chain reaction (HT-qPCR) and qPCR, were used. HT-qPCR is a thermocyclic polymerase chain reaction with high-temperature denaturation, low-temperature denaturation and moderate-temperature extension by adding fluorescent groups to PCR reaction system of template DNA (Su et al., 2015).

Eventually, a total of 290 data points from 60 reservoirs, consisting of 210 water samples and 80 sediment samples, were extracted from 25 studies. Some of the collected parameters (e.g., bacterial communities and nutrient concentrations) were not included in this dataset because only a small number of studies reported it. Thus, in addition to ARG abundance, our dataset consists of 13 explanatory variables including geographic location of sampling sites, reservoir characteristics, seasonal variation, quantitative methods used to measure ARGs, MGE, abundance, and physicochemical indicators (Table S1).

2.2. Statistical analysis

GeoDetector is a new statistical tool for the detection of impact mechanisms as well as risk hotspots (Wang et al., 2010). Compared to traditional correlation and regression analysis, GeoDetector model identifies driving forces of multiple independent variables (x_i) on the dependent variable (y) and their interactions and does not require linear assumptions (Guo et al., 2021a). We used the GeoDetector model to quantify effects of the 13 explanatory variables (geographic location, seasonal variation, reservoir characteristics, physicochemical parameters, and quantitative methods) on ARGs and their interactions (Fig. 1b). A detailed description of GeoDetector models is in Text S2.

Of the 13 independent variables, those identified as having a significant effect (q-value: $p < 0.05$) by GeoDetector model’s factor detector were further analyzed to assess driving patterns of differences in the distribution of ARGs. Linear or binomial regressions were chosen to fit two-variable on the R^2 and Akaike Information Criterion (AIC) (Burnham and Anderson, 2002). Combined with the results from the GeoDetector model’s risk detector, we assessed subregions with the highest potential risk or patterns favoring distributions of ARGs. Because absolute abundance reflects the true number and variance of ARGs in the sample, we used absolute abundance of ARGs when available for factor detection and fitted regression analyses (150 water samples and 46 sediment samples).

Analysis of Similarities (ANOSIM) was used to test whether environmental media (water vs sediment) cause differences in ARG distribution. Distance Decay models were applied to analyze effects of geographical distance on similarity of ARGs (1-Bray-Curtis) and degree of decay. Mantel tests were used to verify whether distance-decay relationship was significant. If correlations existed, they were fitted using the “vegan” and “SoDA” packages in R software.

3. Results

3.1. Distribution and occurrence of ARGs in reservoirs

ARG abundance data were collected from a total of 290 samples in 60 reservoirs covering 4 geographical regions from 40 cities (Fig. 2a,c). To our knowledge, no studies investigating ARG pollution have been conducted in reservoirs located in Africa, North America, or Oceania. Environmental media studies were mainly reservoir waters (22 articles) and sediments (10 articles), with less attention paid to aquatic organisms such as fish (1 article).

The number of ARGs detected per sample varied widely, ranging from 3 to 436. These dominant ARGs fell mainly into 9 classes including ARGs against aminoglycosides, β-lactams, chloramphenicol, macrolide-lincosamide-streptogramin B (MLSB), sulfonamides, tetracyclines, vancomycin, multi-drug resistance, and others. The highest frequency of detection in water samples was for β-lactams and MLSB resistance genes (155/210, both 74%), followed by tetracyclines (72%), sulfonamides (69%), aminoglycosides (64%), and multi-resistance genes (53%). The highest frequency of detection in sediments was for tetracyclines (50/80, 63%), followed by sulfonamides (48%) and MLSB resistance genes

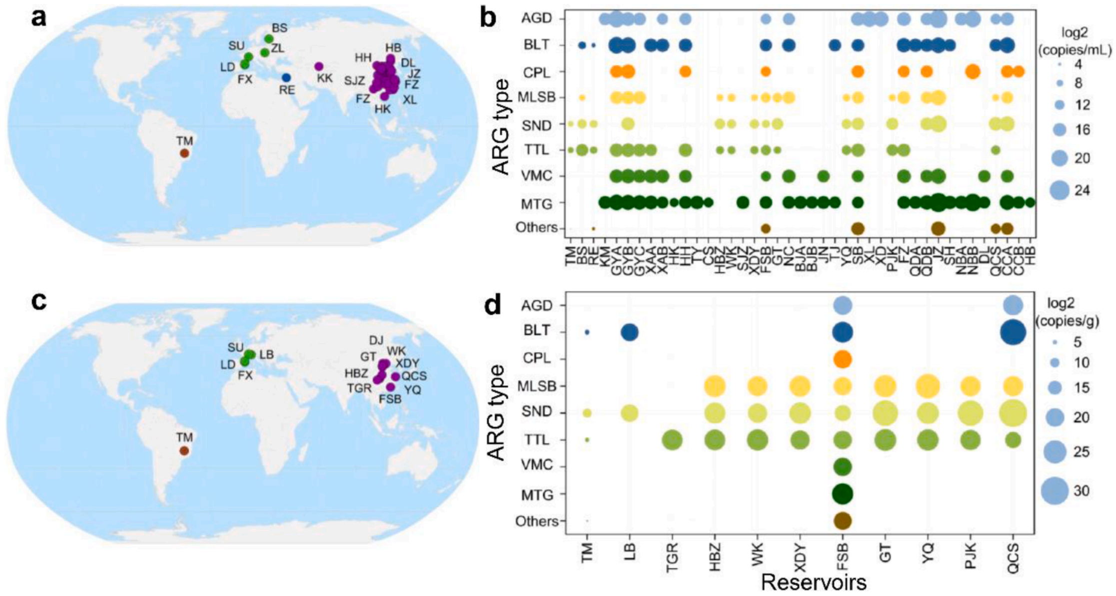

Fig. 2. Distribution of samples (a = waters and c = sediments) for antibiotic resistance genes (ARGs) in reservoirs and absolute abundance (log2) of ARGs in waters (b) and sediments (d) of individual reservoirs. ARG types: AGD – aminoglycosides, BLT – β-lactams, CPL – chloramphenicol, MLSB – macrolide-lincosamide-streptogramin B, SND – sulfonamides, TTL – tetracyclines, VMC – vancomycin, MTG – multi-drug resistance. Abbreviations of reservoir name can be found in Table S1 (Basic information).

(44%).

Abundance and most common classes of dominant ARGs varied among reservoirs (Fig. 2b,d). Absolute abundance of ARGs detected in waters of the Três Marias Reservoir (TM; Brazil, South America) and Hadera Reservoir (RE; Israel, Middle East) were low with 2.77×10^2 copies/mL and 7.40×10^2 copies/mL, respectively. Sulfonamide and tetracycline resistance genes were the main classes of ARGs in these two reservoirs. In the European region (BS; Fig. 2b), absolute abundance of ARGs detected in reservoir waters ranged from 2.21×10^4 to 8.94×10^4 copies/mL (average value: 3.30×10^4 copies/mL), with the highest abundance being tetracycline resistance genes, followed by ARGs for sulfonamides and β-lactams. In the Asian region, the average absolute abundance of ARGs in reservoir waters was one order of magnitude higher than in Europe with 7.77×10^5 copies/mL (range 1.93×10^3–1.56×10^7 copies/mL). Multi-drug resistance genes were most abundant in Asian reservoir waters, followed by aminoglycoside and sulfonamide resistance genes. Consistent with the absolute abundance results, relative abundance of ARGs in European reservoir waters was low, with multi-drug resistance and aminoglycoside resistance genes being the dominant ARGs (Fig. S1a). Relative abundance of all 9 ARG classes detected in reservoir waters was low (average value: 0.02 copies/16S rRNA).

Variation of ARG abundance in reservoir sediments was greater (Figs. 2d and S1b) than the variation in water. The lowest abundance of ARGs was detected in Três Marias Reservoir (8.97×10^2 copies/g; Brazil, South America), followed by Lake Brêt in Europe (1.13×10^6 copies/g; Switzerland). The highest levels of ARGs were detected in reservoir sediments from Asia with an average abundance of 2.37×10^8 copies/g. Reservoir sediment samples had a high proportion of sulfonamide and β-lactam resistance genes. In addition, MLSB resistant genes were also detected in high abundances in Asian reservoir sediments (Fig. 2d). Average relative abundance of all 9 ARG classes was <0.01 copies/16S rRNA (Fig. S1b).

3.2. Factors and their interactions

As shown by the Analysis of Similarity (ANOSIM), environmental media influenced composition of reservoir ARGs ($r = 0.62$, $p < 0.01$), and differences in composition of ARGs were significantly higher in waters than in sediments (Fig. S2). Similarity of ARG composition followed a distance-decay relationship in both reservoir waters and sediments (Mantel test: waters $r = 0.39$, $p < 0.01$; sediments $r = 0.50$, $p < 0.01$). Similarity of ARG composition in waters exhibited a higher decay rate with increasing geographical distance compared to sediments (slope: $1.99 \times 10^{-5} > 1.14 \times 10^{-5}$; Fig. 3a,b).

Thirteen potential variables such as geographic location, seasonal variation, physicochemical parameters, reservoir characteristics, and quantitative methods of ARGs influenced differences in distribution of ARG concentration (Fig. S2a). Among them, mobile genetic elements (MGEs; explanatory power: 87%), reservoir capacity (55%), water temperature (54%), and reservoir catchment area (47%) were the dominant factors influencing distribution of ARGs in reservoir waters. Antibiotic concentration (17%) was secondary in explaining variation in the distribution of ARGs. Effects of quantitative methods (qPCR versus HT-qPCR) and total organic carbon (TOC) on the variation of ARGs in waters were significant but weak, with both being below 10%. In terms of factor interactions, some single factors such as geographical location and seasonal variation, had no significant impact on ARGs, but these parameters often showed significant two-factor linear or non-linear enhancement effects with other parameters. For example, interactions of longitude ∩ water temperature (the interaction of factors X_1 and X_2 is represented by $X_1 \cap X_2$), longitude / latitude ∩ MGEs, seasonal variation ∩ MGEs, seasonal variation ∩ reservoir catchment area, and seasonal variation ∩ water temperature all explained over 83% of differences in distribution of ARGs.

In reservoir sediments, factors that dominated differences in distribution of ARGs were reservoir characteristics, geographical location, and physicochemical parameters (Fig. S2b). Among them, reservoir catchment area, reservoir level, and longitude had the strongest influence on ARGs with all explaining over 69% of the variation. TOC, pH, and reservoir capacity were also important factors driving differences in distribution of ARGs, followed by MGEs and antibiotic concentrations ($\geq$ 26%). Except for effects of antibiotic concentration and quantification method on ARGs, which were independent of each other, all other factors together increased the explanatory power of differences in ARG distribution. In particular, two-factor linear enhancement effects of seasonal variation ∩ reservoir level, seasonal variation ∩ reservoir catchment area, longitude ∩ seasonal variation, longitude ∩ TOC,

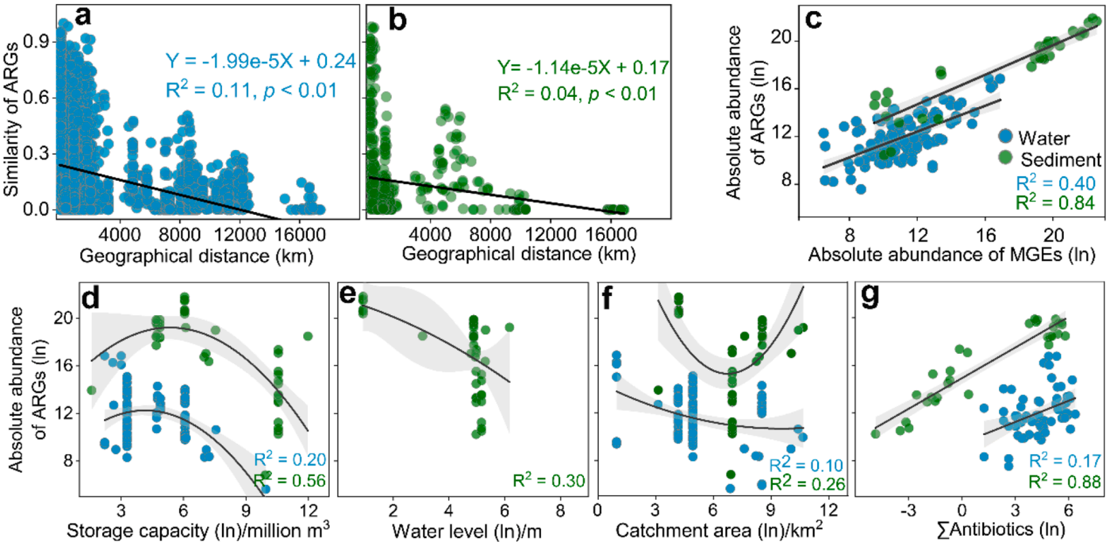

Fig. 3. Distance decay of ARGs similarity (1-Bray-Curtis) in reservoir waters (a) and sediments (b) and relationship between ARGs and influencing factors (c to g). Regression line (solid line) and R^2 are shown only if the bivariate relationship is statistically significant ($p < 0.05$). Unfitted indicate that binomial fit is not significant or bivariate is not correlated. Shaded areas are 95% confidence intervals.

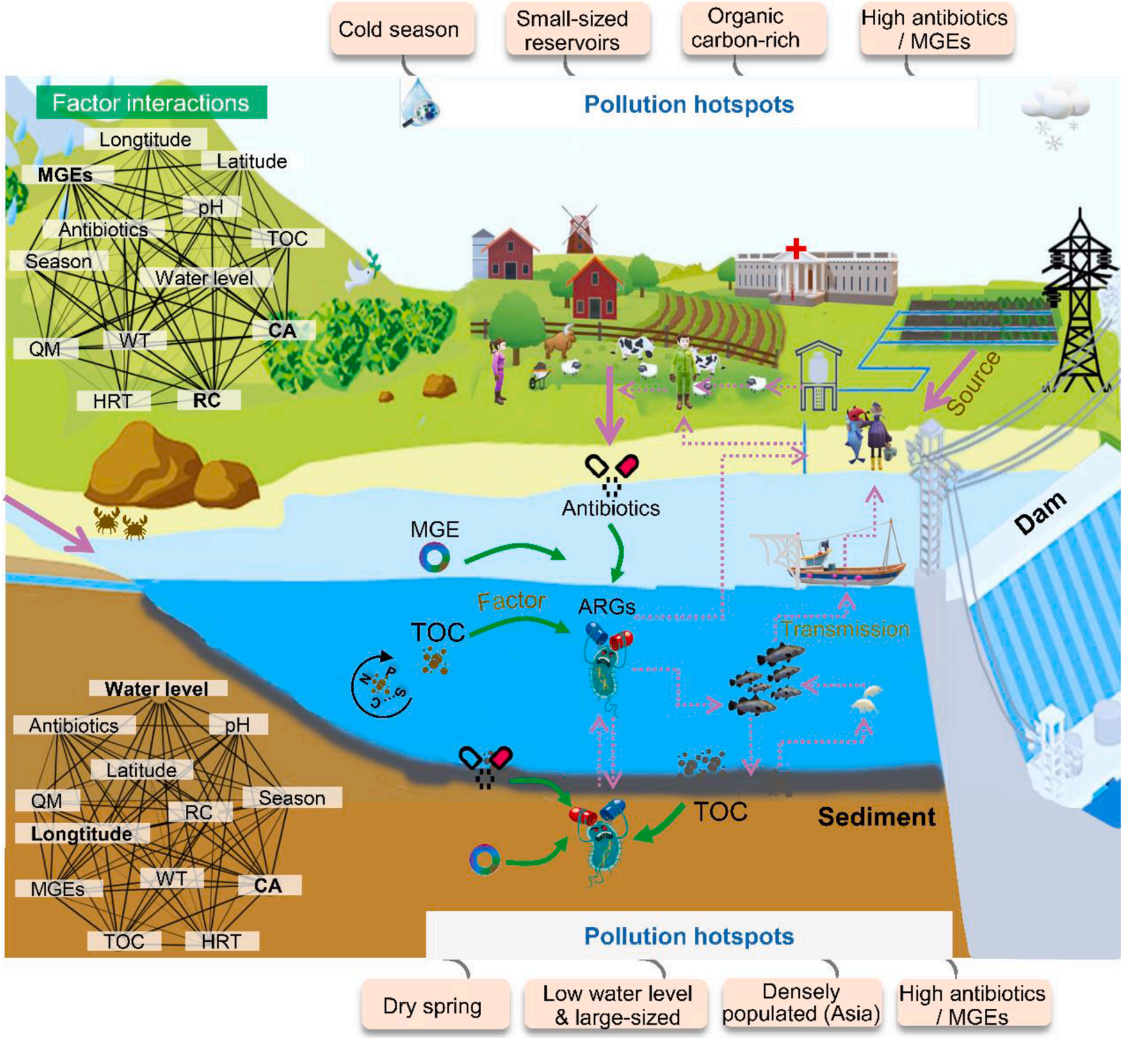

Fig. 4. Pollution paradigm of ARGs in reservoirs. MGEs – mobile genetic elements, RC – reservoir capacity, CA – reservoir catchment area, WT – water temperature, TOC – total organic carbon, QM – quantification method of ARGs, HRT – hydraulic residence time.

reservoir level ∩ TOC, and reservoir catchment area ∩ TOC, and a nonlinear enhancement effect of MGEs ∩ TOC all drove up the explanatory power to above 80%.

3.3. Models and pollution paradigm

Relationships between dominant factors and ARG abundance were further quantified using regression analyses. Abundance of reservoir ARGs showed a linear relationship with both MGEs and antibiotic concentrations (Fig. 3c,g). Similarly, abundance of ARGs in sediments increased with increasing longitude (Fig. S3). However, reservoir characteristics (reservoir capacity, reservoir level, and reservoir catchment area) were not simply linearly related to ARGs (Fig. 3d–f). Absolute abundance of ARGs in waters and sediments increased and then decreased with reservoir capacity, while the relationship with reservoir catchment area had an opposite trend, showing a decrease followed by an increase. Abundance of ARGs in waters increased with TOC, while abundance of ARGs in sediments showed a decreasing and then increasing trend with TOC and pH (Fig. S3). In addition, water temperature, an important factor influencing ARG abundance distribution in waters, did not show a significant linear relationship with ARG abundance, indicating that the relationship was complex and needs to be further identified in conjunction with results from risk detection.

Pollution hotspot of ARGs in reservoirs was assessed by combining regression analyses and GeoDetector model's risk detection (Fig. 4). Reservoirs with small storage capacity and catchment areas were more likely to have enriched ARGs in waters, while larger reservoir capacity and low reservoir levels indicated high susceptibility to ARG contamination in reservoir sediments. Additionally, low-temperature seasons (winter or early spring) contributed to enrichment of ARGs in reservoir waters, while dry spring seasons predispose reservoirs to ARG contamination in sediments, especially when situated close to coastal cities in China (densely populated areas). Reservoir waters rich in TOC and with higher abundance of antibiotics and MGEs had relatively higher abundance of ARGs. Similarly, the higher the residual antibiotic and MGEs in sediments, the more abundant were ARGs.

4. Discussion

4.1. Spatial variations and factors influencing difference of ARGs

Typical classes and abundance of widespread ARGs in reservoirs varied across continents and reservoirs. Different levels of ARG contamination have been detected in reservoirs from 4 geographic regions to date. The amount of ARGs detected varied across reservoirs by 1–2 orders of magnitude and their classes varied as well. In South America and the Middle East, abundance of ARGs detected in reservoir waters was low and was dominated by sulfonamide and tetracycline resistance genes. In contrast, probably due to higher population densities and prevalent over-consumption of antibiotics (Klein et al., 2018), reservoir waters in Asia were the most contaminated by ARGs, with concentrations an order of magnitude higher than in Europe. Multi-drug, aminoglycoside, and sulfonamide resistance genes were the most abundant types in Asia's reservoirs.

Reflecting concentrations in water, ARG contamination in sediments was also relatively low in South America, followed by the European region, while Asia was the most polluted. In some reservoir sediments (e.g., Danjiangkou; DJ), dominant gene classes were not consistent with those in waters. This might indicate that common antibiotics used in various geographical regions have changed over time and the sediment serves as a "memory" of past activities (Anderson, 1995) or that certain antibiotics have a higher affinity to the sediment (Löffler et al., 2005) and thus the corresponding ARGs are also preferably found there. In general, geographical differences in ARG contamination may be attributed to local differences in antibiotic production and consumption patterns and disposal levels (Gilchrist et al., 2007; Van Boeckel et al., 2014). This suggests that contamination in reservoir ARGs requires place-based control strategies to improve water supply and ecological security. To date, no data have been collected on occurrence of ARGs in reservoir waters and sediments from Africa, North America, and Oceania, which should become a research priority in those regions.

Similarity of ARGs decreased with increasing geographical distance. This suggests that reservoirs, that are closely located or have overlapping pollution sources are more likely to transmit or receive the same ARGs. Distance-decay rates reflect limitations in dispersal of microbial communities (Martiny et al., 2006). However, similarity of ARGs in waters exhibited a higher rate of geographical distance-decay than sediments., i.e., microbes in sediments and their ARGs are capable of dispersing more readily than microbes in waters. We believe this can be attributed to long-term sediment deposition and accumulation and microbial communities in sediments are relatively stable (Iniesto et al., 2021), which is conducive to dispersal of ARGs over time. Because of limited data available for monitoring ARGs in reservoir sediments, future studies will need more information to verify this interesting speculation.

Factors driving distribution of ARG abundance in reservoirs and the degree of their influence differed in water versus sediment. Variations in distribution of ARGs in reservoir waters were significantly higher than those in sediments, which may be attributed to the more complex and diverse sources of ARGs in reservoir waters with frequent anthropogenic disturbances. MGEs, reservoir capacity, water temperature, and reservoir catchment area were important factors influencing ARG distribution in waters, while in sediments reservoir characteristics (reservoir catchment area, reservoir level, and reservoir capacity), longitude, TOC, and pH were the most important influencing factors. Reservoir characteristics influenced ARG distribution most strongly, however, relationships between reservoir and ARG abundance in reservoirs was not simply linear. This suggests that characteristics of ARG distribution in reservoirs were the result of a multifactorial interaction. In other words, ARGs that enter reservoirs can interact with multiple abiotic, reservoir-internal factors in complex manners, which in turn expose reservoir ecosystems to new and poorly understood stressors with the possibility of unintended repercussion for biota and humans.

Furthermore, interactions between factors often resulted in linear or nonlinear enhancement effects on the distribution of ARGs (Fig. 4). Such interactions occurred namely between similar parameters (e.g., antibiotics ∩ TOC, which are both chemical parameters) and also between vastly different variables (e.g., seasonal variation ∩ reservoir capacity). Although ARGs in reservoirs did not show significant seasonal variation, seasonal factors together with reservoir characteristics and MGEs had a strong influence on ARGs of reservoir waters. Likewise, seasonal variation together with reservoir level and longitude explain a significant amount of variation of ARGs in reservoir sediments. Joint effects of seasonal variation and reservoir characteristics on ARGs distribution may originate from the fact that reservoir dynamic capacity (or water levels) fluctuate seasonally due to drawing of water resources from the reservoir during scheduled time periods (Soundharajan et al., 2016). This dynamic process may enhance influence on reservoir ARG composition and their occurrence. In addition to the influence of reservoir characteristics, we also found that the seasonal factors coupled with longitudinal gradient variables reflecting demographic and economic differences act together in the distribution of ARGs in sediments. Sediment samples were mainly collected from reservoirs in China, and the region shows a trend of increasing population and economy with increasing longitude from west to east (Zhang et al., 2022). The enhanced interaction of seasonal variation ∩ longitude suggests certain seasonal variation in ARG pollution in densely populated areas.

To understand the actual influence mechanisms, integrated monitoring of reservoir characteristic parameters and consideration of the combined effects of multiple variables on reservoir ARGs are required. That needs to go hand in hand with a more uniform utilization of methodologies. For example, compared to HT-qPCR methods, the amount and classes of ARGs detected in waters by qPCR methods were limited (Yang et al., 2018). Dominant ARGs were analyzed in this study, and overall, quantifying method of ARGs had small effects on the total abundance of dominant ARGs.

Both, high abundance of antibiotics and MGEs, contributed to increased ARGs. Under the selective pressure of antibiotics, a large quantity of antibiotic resistant bacteria can be transferred through MGEs and thus disseminate ARGs (Zainab et al., 2020). Hence, rational use of antibiotics, proper disposal of antibiotic waste and wastewater, and widespread public education about antibiotic drugs will help mitigate contamination from ARGs (Chung and Brooks, 2019).

4.2. Pollution hotspots of ARGs

We identified potentially contaminated areas of ARGs in reservoirs, which provides a base for more focused future investigations of ARG pollution management in reservoirs. As both, the demand for reservoir ecosystem services and the risk of ARG pollution increase, it is essential to improve our understanding of ARG contamination and be able to tailor pollution mitigation strategies according to characteristics of specific reservoirs. Thus, we strived to clarify pollution potential of ARGs in reservoir waters and sediments by considering effects of multiple risk factors such as spatiotemporal heterogeneity as well as reservoir characteristics.

ARGs in reservoir waters and sediments had different pollution hotspots (Fig. 4). In waters, small-sized reservoirs, rich in organic carbon were more vulnerable to contamination by ARGs, especially during the cold season. Seasonal anthropogenic activities and climate effects, such as increased use of antibiotic treatments to treat or prevent human and livestock diseases in the cold season, may lead to more serious contamination of ARGs during that time (Suda et al., 2014). Abundance of organic carbon in reservoir waters can lead to an increase in ARGs because ARGs can bind to organic carbon and protect them from degradation by nucleases (Demaneche et al., 2001). Alternatively, higher organic carbon favors the proliferation of heterotrophic bacteria and these bacteria are more likely to carry intracellular ARGs (Tuomanen et al., 1986). Thus, for small-sized reservoirs with high organic carbon content and during the cold season, the pollution discharge has to be closely monitored and potentially mitigated especially when intending to use the water for human consumption. This can be particularly critical since the storage capacity is small and the amount of available drinking water may be limited.

ARGs in sediments were dependent on geographical location and overall concentration of antibiotics in sediments. In densely populated areas, production of ARGs in large reservoir sediments may be induced by more widespread antibiotic production and consumption. A spring drought reduces the dilution effect on contaminants and a relative increase in the level of contaminants such as antibiotics in reservoir sediments can generate higher selective pressure on microorganisms (Dang et al., 2020). Therefore, it should be possible to respond to ARG contamination by regulating the water level of reservoirs during this time period.

Pollution risk assessments regarding reservoirs' ARGs are limited. Consequently, it is necessary to construct a risk assessment system across ecosystems, especially pollution hotspots. Reservoirs are critical water supply infrastructures and contamination of reservoirs by ARGs not only damages the structure and function of reservoir ecosystems, but also threatens human health through direct and food-chain transmission. To build a risk assessment system for ARGs, it is necessary to work together at the international level to promote global and interdisciplinary communication and assistance at the human - food-chain - ecosystem interface to address general public health as advocated for by the "One Health" perspective (Zhu et al., 2019). This will improve both, awareness and understanding of antibiotic resistance risks, and make an implementation of best management practices to maintain multiple reservoir services possible. In addition, this would support the goals laid out in the UN Sustainable Development Goals (United Nations, 2015) to secure basic physical needs and health benefits of humanity. Overall, considering the potential for transfer of ARGs from the environment over organismal hosts to become human pathogens, we believe that the hierarchical risk system as proposed by Martinez et al. (2015) would work well to distinguish between public health risks of different classes of ARGs.

4.3. Challenges and prospects

We used a data-driven framework (DD) to integrate the distribution, influencing factors, and pollution hotspots of ARGs from a total of 60 reservoirs in 4 geographic regions. This allowed us to identify spatiotemporal ranges and indicator variables that need to be monitored as a priority for reservoir ARG studies in the future. Contamination potential of ARGs in water was higher in small-sized reservoirs, rich in organic carbon and antibiotics, especially during the cold season. Unlike reservoir waters, sediments of large reservoirs in densely populated areas had a higher potential of ARG contamination due to the residual and accumulation of antibiotics over a long time. Pollution hotspots of ARGs were identified at the intercontinental scale, which helps to systematically set priorities for pollution monitoring and control of reservoir ARGs in areas with high risk of contaminants. Although the currently limited amount of data is not sufficient to reflect the full picture of ARG contamination in reservoirs, the DD framework may be further improved to assess reservoirs' ARG contamination and its pollution hotspots as more and more detailed data become available. Therefore, the constructed DD framework can be upgraded and optimized for data grouping and statistics in future as additional data continue to emerge. This provides a heuristic and replicable research paradigm for data-intensive scientific discoveries of environmental pollutants in terms of systematic methodology, dataset integrity, and scientific discoveries.

Large-scale investigations of ARGs in reservoirs are currently underway, but there is still a need to expand the scope of ARG studies in reservoirs and obtain more field monitoring data in order to establish a complete international monitoring system. In particular, Africa, North America, South America, and Oceania have not yet or rarely been screened for occurrence of ARGs in their reservoirs. In these regions, no or too few sample data have been obtained to provide a comprehensive understanding of their ARG pollution status. In Asia and Europe, pollution of reservoir ARGs is of higher concern and more closely monitored in at least some reservoirs. However, considering the increasing antibiotic use and antibiotic resistance (aus der Beek et al., 2016; Zhao et al., 2020) as well as the important ecosystem service of reservoirs, it is necessary to expand the geographical scope of reservoir investigations globally. Additionally, the problem of ARG pollution might be unknowingly greatly exacerbated in some less developed regions or countries with poor water quality and sanitation (Larsson and Flach, 2022), which are typical hotspots for antibiotic resistance transmission (Nadimpalli et al., 2020). Nevertheless, ARGs do not respect national boundaries and tend to propagate rapidly around the world (Hooban et al., 2020; Okeke and Edelman, 2001). Consequently, challenges regarding ARG contamination of reservoirs require a broad international and interdisciplinary collaboration to include a global perspective. This will not only improve understanding of general antibiotic resistance, but also help less developed countries to focus on most important monitoring efforts and effective treatment of ARG contamination, thus building a reliable and complete monitoring system with minimal resources.

In view of the various influencing factors of ARG pollution in reservoirs, we should incorporate the identified important variable into a standardized data monitoring system to comprehensively assess pollution mechanisms of ARGs. In other words, future pollution surveys of ARGs in individual reservoirs need to consider the effects and interactions of sampling location, reservoir characteristics, seasonal variation, and physicochemical parameters (including water temperature, pH, antibiotic concentration, and TOC). Furthermore, bacterial communities facilitate ARGs transfer (Shin et al., 2020) and effects of their biomass and community composition on ARGs in reservoirs deserve further investigation. In our study, we did not focus on impacts of bacterial communities on ARGs in reservoirs due to the limited data availability. In addition to some well-documented selective pressures on antibiotics, some non-antibiotic pollutants such as metals, polycyclic aromatic hydrocarbons (PAHs), and disinfectants often contribute to proliferation and dissemination of ARGs (Ostman et al., 2017; Zhu et al., 2013). Interestingly, reservoirs serve as important storage sites for nutrients (Guo et al., 2021b), and algal blooms triggered by excess nutrients may instead inhibit proliferation of ARGs (Guo et al., 2018). Thus, it is necessary to integrate these biotic and abiotic parameters for future pollution monitoring for ARGs in reservoirs in order to make accurate judgments about parameters driving ARGs.

Ecological and health risks of antibiotic resistance in reservoirs need to consider not only contamination of ARGs within reservoir ecosystems, but also determine risks posed by transmission of antibiotic-resistant bacteria through food chains and by resistance of human commensal microorganisms. ARGs have the ability to disseminate through water supply systems to a healthy gut flora of humans (Zhu et al., 2018). Yet, it is unclear whether reservoirs' ARGs and antibiotic resistant bacteria actually have a substantial impact on human exposure to ARG contamination. To monitor and assess risks, data on antibiotic use and residues, ARG types of human accessibility, antibiotic-resistant bacteria in faces and gut, and ARGs need to be collected to integrate environmental, biological, and human transmission pathways and risk potential (Huijbers et al., 2019; Wilkinson et al., 2022; Zhang et al., 2022). Only by fully understanding the emergence, spread, and evolution of ARGs within the reservoir – food-chain – human pathway can we start to grasp the overall impact of ARGs on health risk and take appropriate actions (Hernando-Amado et al., 2019). Advancement of gene sequencing technologies offers the possibility to track and quantify transmission risk of this complex pathway and to find key control points for dissemination of antibiotic-resistant bacteria (Koch et al., 2017). This will not only allow for a better understanding of antibiotic resistance transmission mechanisms on the cross-ecosystem scale, but also improve contamination monitoring and risk control strategies for ARGs. Applying quantitative microbial risk assessment (QMRA) methods, the health risks posed by exposure to ARGs and antibiotic-resistant bacteria in reservoir ecosystems can be determined (Amarasiri et al., 2019).

Standardized sampling methods and detailed records (location, reservoir characteristics, sampling effort, weather and climate condition, etc.), would improve study comparability and reduce uncertainties in findings. During the extraction of literature data, we found that some studies lacked information such as specific coordinates of sampling sites, sampling depth, sampling time, and reservoir characteristics. Moreover, units of ARG measurements were not uniform. Results of this study demonstrated that these parameters were influential on how ARGs were generally distributed. In addition, parameters such as nutrients and land use were important drivers of changes in ARG distribution (Pei et al., 2006; Subirats et al., 2018). In particular, information on ARGs and antibiotic discharges from point / diffuse sources such as wastewater treatment plants, pharmaceutical plants and livestock farms around reservoirs is key to identify occurrence and potential sources of ARG compositions (Li et al., 2020), but relevant background information is less commonly mentioned. Relationships between certain environmental factors and ARGs in reservoirs could not be quantified and assessed because often these important parameters were ignored or too many data were missing. The lack of study comparability reduces data availability and ultimately results accuracy. Therefore, standardized reporting and detailed documentation of these parameters would allow for more usable data to support analyzes of ARG pollution in future.

We strongly encourage international data sharing to improve data availability, accessibility, and large-scale, reproducible analyses. This would promote convergence of disciplines while simultaneously expanding and directing important research foci of ARGs. The existing ARG classes in reservoirs are diverse and complex, and costs of monitoring them qualitatively and quantitatively are large. However, at the same time, the amount of data information generated would be substantial. Furthermore, we then could merge all of the data on an information sharing platform and exchange data supporting the 'Science without Borders' vision (Laursen, 2018). This large data resource would greatly facilitate and increase information we could extract from these data. Access and reanalysis of shared raw data by scientists across disciplines and borders could greatly extend the depth of ongoing research and reduce the amount of research repetition required (Prince et al., 2020; Tedersoo et al., 2021). However, data requests to authors were often ignored or eventually remained unanswered during our collection of ARG data, presumably caused by cultural, technical, policy, and privacy barriers. Construction of reservoir ARG datasets is not the ultimate goal of this study. Our focus is to find a way to integrate cross-sectoral and interdisciplinary knowledge that can lead to data-intensive scientific discoveries. Therefore, steps to encourage data sharing and accessibility should be prioritized during policy, management, and technology development (Alexander et al., 2019; Li et al., 2021). This would enable statisticians and scientists with the ability and willingness to analyze large data sets to more effectively address needs to conduct research and manage ARGs pollution across a large scale in reservoirs as well as similar issues.

In summary, the six priorities for future research to better understand pollution and potentially contaminated areas of ARGs in reservoirs on a global scale are: (i) prioritizing controlling reservoirs with high-pollution potential; (ii) expanding global monitoring of reservoirs' ARG pollution and building effective monitoring systems based on international interdisciplinary collaboration; (iii) incorporating identified determining factors into data collection of ARGs in reservoirs data monitoring systems; (iv) quantifying risks from ARGs through reservoir – food-chain – human pathways; (v) standardizing sampling methods and detailing survey report formats; (vi) encouraging data sharing, improving data accessibility and providing of a finer resolution of existing data.

5. Conclusion

A data-driven framework was constructed to systematically demonstrate distribution, influencing factors, and potentially contaminated areas of ARGs in reservoirs at the intercontinental scale. In the conducted studies, dominant classes and abundance of ARGs detected varied among continents and reservoirs. The most ARGs contaminated reservoirs were located in Asia. Factors affecting difference in occurrence and distribution, such as reservoir characteristics and physicochemical indicators, often interacted and showed linear or nonlinear enhancement effects on ARGs both in waters and sediments. Small-sized reservoir waters rich in organic carbon and antibiotics have a higher pollution potential of ARGs during the cold season, while larger reservoir sediments contribute to accumulation and dissemination of ARGs during spring drought. Considering the multiple ecosystem service functions reservoirs provide and the health hazards of ARG contamination and their antibiotic resistance, future research needs to include expanded monitoring and prioritize control of ARGs in high-risk areas. The most important influencing factors of ARGs in reservoirs should be incorporated into routine monitoring of reservoirs. Particular emphasis needs to be on integrated risk of ARG transmission via the reservoir ecosystem – food-chain – human pathway. Furthermore, detailed information such as sampling specifics and reservoir characteristics need to be documented to allow comparison among studies and data be made accessible to allow for broad global analyses

Declaration of Competing Interest

We declare that we do not have any commercial or associative interest that represents a conflict of interest in connection with the work submitted.

Data Availability

Data will be made available on request.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.watres.2022.119466.

References

Alexander, S.M., Jones, K., Bennett, N.J., Budden, A., Cox, M., Crosas, M., Game, E.T., Geary, J., Hardy, R.D., Johnson, J.T., Karcher, S., Motzer, N., Pittman, J., Randell, H., Silva, J.A., da Silva, P.P., Strasser, C., Strawhacker, C., Stuhl, A., Weber, N., 2019. Qualitative data sharing and synthesis for sustainability science. Nat. Sustain. 3 (2), 81–88. https://doi.org/10.1038/s41893-019-0434-8.

Amarasiri, M., Sano, D., Suzuki, S., 2019. Understanding human health risks caused by antibiotic resistant bacteria (ARB) and antibiotic resistance genes (ARG) in water environments: current knowledge and questions to be answered. Crit. Rev. Environ. Sci. Technol. 50 (19), 2016–2059. https://doi.org/10.1080/10643389.2019.1692611.

Anderson, N.J., 1995. Using the past to predict the future: lake sediments and the modelling of limnological disturbance. Ecol. Model. 78 (1-2), 149–172. https://doi.org/10.1016/0304-3800(94)00124-Z.

aus der Beek, T., Weber, F.A., Bergmann, A., Hickmann, S., Ebert, I., Hein, A., Kuster, A., 2016. Pharmaceuticals in the environment—global occurrences and perspectives. Environ. Toxicol. Chem. 35 (4), 823–835. https://doi.org/10.1002/etc.3339.

Bengtsson-Palme, J., Kristiansson, E., Larsson, D.G.J., 2018. Environmental factors influencing the development and spread of antibiotic resistance. FEMS Microbiol. Rev. 42 (1) https://doi.org/10.1093/femsre/fux053.

Berendonk, T.U., Manaia, C.M., Merlin, C., Fatta-Kassinos, D., Cytryn, E., Walsh, F., Burgmann, H., Sorum, H., Norstrom, M., Pons, M.N., Kreuzinger, N., Huovinen, P., Stefani, S., Schwartz, T., Kisand, V., Baquero, F., Martinez, J.L., 2015. Tackling antibiotic resistance: the environmental framework. Nat. Rev. Microbiol. 13 (5), 310–317. https://doi.org/10.1038/nrmicro3439.

Burnham, K.P., Anderson, D.R., 2002. Model Selection and Multimodel Inference: A Practical Information-Theoretic Approach, 2nd ed. Springer-Verlag, New York.

Chatterjee, A., Modarai, M., Naylor, N.R., Boyd, S.E., Atun, R., Barlow, J., Holmes, A.H., Johnson, A., Robotham, J.V., 2018. Quantifying drivers of antibiotic resistance in humans: a systematic review. Lancet Infect. Dis. 18 (12), e368–e378. https://doi.org/10.1016/s1473-3099(18)30296-2.

Chen, Y.H., Li, P., Huang, Y.S., Yu, K.F., Chen, H.J., Cui, K.P., Huang, Q.L., Zhang, J.Y., Gin, K.Y.H., He, Y.L., 2019. Environmental media exert a bottleneck in driving the dynamics of antibiotic resistance genes in modern aquatic environment. Water Res. 162, 127–138. https://doi.org/10.1016/j.watres.2019.06.047.

Chung, S.S., Brooks, B.W., 2019. Identifying household pharmaceutical waste characteristics and population behaviors in one of the most densely populated global cities. Resour. Conserv. Recycl. 140, 267–277. https://doi.org/10.1016/j.resconrec.2018.09.024.

Dang, C.Y., Xia, Y., Zheng, M.S., Liu, T., Liu, W., Chen, Q., Ni, J.R., 2020. Metagenomic insights into the profile of antibiotic resistomes in a large drinking water reservoir. Environ. Int. 136 (10) https://doi.org/10.1016/j.envint.2019.105449.

Demaneche, S., Jocteur-Monrozier, L., Quiquampoix, H., Simonet, P., 2001. Evaluation of biological and physical protection against nuclease degradation of clay-bound plasmid DNA. Appl. Environ. Microbiol. 67 (1), 293–299. https://doi.org/10.1128/AEM.67.1.293-299.2001.

Garner, E., Chen, C., Xia, K., Bowers, J., Engelthaler, D.M., McLain, J., Edwards, M.A., Pruden, A., 2018. Metagenomic characterization of antibiotic resistance genes in full-scale reclaimed water distribution systems and corresponding potable systems. Environ. Sci. Technol. 52 (11), 6113–6125. https://doi.org/10.1021/acs.est.7b05419.

Gilchrist, M.J., Greko, C., Wallinga, D.B., Beran, G.W., Riley, D.G., Thorne, P.S., 2007. The potential role of concentrated animal feeding operations in infectious disease epidemics and antibiotic resistance. Environ. Health Perspect. 115 (2), 313–316. https://doi.org/10.1289/ehp.8837.

Guo, Y.Y., Liu, M., Liu, L.M., Liu, X., Chen, H.H., Yang, J., 2018. The antibiotic resistome of free-living and particle-attached bacteria under a reservoir cyanobacterial bloom. Environ. Int. 117, 107–115. https://doi.org/10.1016/j.envint.2018.04.045.

Guo, Z.F., Boeing, W.J., Xu, Y.Y., Borgomeo, E., Mason, S.A., Zhu, Y.G., 2021a. Global meta-analysis of microplastic contamination in reservoirs with a novel framework. Water Res. 207, 117828 https://doi.org/10.1016/j.watres.2021.117828.

Guo, Z.F., Boeing, W.J., Xu, Y.Y., Yan, C.Z., Faghihinia, M., Liu, D., 2021b. Revisiting seasonal dynamics of total nitrogen in reservoirs with a systematic framework for mining data from existing publications. Water Res. 201, 117380 https://doi.org/10.1016/j.watres.2021.117380.

Hendriksen, R.S., Munk, P., Njage, P., van Bunnik, B., McNally, L., Lukjancenko, O., Roder, T., Nieuwenhuijse, D., Pedersen, S.K., Kjeldgaard, J., Kaas, R.S., Clausen, P.T. L.C., Vogt, J.K., Leekitcharoenphon, P., van de Schans, M.G.M., Zuidema, T., de Roda Husman, A.M., Rasmussen, S., Petersen, B., , The Global Sewage Surveillance project consortium, Amid, C., Cochrane, G., Sicheritz-Ponten, T., Schmitt, H., Alvarez, J.R. M., Aidara-Kane, A., Pamp, S.J., Lund, O., Hald, T., Woolhouse, M., Koopmans, M.P., Vigre, H., Petersen, T.N., Aarestrup, F.M., 2019. Global monitoring of antimicrobial resistance based on metagenomics analyses of urban sewage. Nat. Commun. 10 (1), 1124. https://doi.org/10.1038/s41467-019-08853-3.

Hernando-Amado, S., Coque, T.M., Baquero, F., Martinez, J.L., 2019. Defining and combating antibiotic resistance from one health and global health perspectives. Nat. Microbiol. 4 (9), 1432–1442. https://doi.org/10.1038/s41564-019-0503-9.

Hooban, B., Joyce, A., Fitzhenry, K., Chique, C., Morris, D., 2020. The role of the natural aquatic environment in the dissemination of extended spectrum beta-lactamase and carbapenemase encoding genes: a scoping review. Water Res. 180, 115880 https://doi.org/10.1016/j.watres.2020.115880.

Huijbers, P.M.C., Flach, C.F., Larsson, D.G.J., 2019. A conceptual framework for the environmental surveillance of antibiotics and antibiotic resistance. Environ. Int. 130, 104880 https://doi.org/10.1016/j.envint.2019.05.074.

Iniesto, M., Moreira, D., Reboul, G., Deschamps, P., Benzerara, K., Bertolino, P., Saghai, A., Tavera, R., Lopez-Garcia, P., 2021. Core microbial communities of lacustrine microbialites sampled along an alkalinity gradient. Environ. Microbiol. 23 (1), 51–68. https://doi.org/10.1111/1462-2920.15252.

Klein, E.Y., Van Boeckel, T.P., Martinez, E.M., Pant, S., Gandra, S., Levin, S.A., Goossens, H., Laxminarayan, R., 2018. Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. Proc. Natl. Acad. Sci. U. S. A. 115 (15), E3463–E3470. https://doi.org/10.1073/pnas.1717295115.

Koch, B.J., Hungate, B.A., Price, L.B., 2017. Food-animal production and the spread of antibiotic resistance: the role of ecology. Front. Ecol. Environ. 15 (6), 309–318. https://doi.org/10.1002/fee.1505.

Laffite, A., Al Salah, D.M.M., Slaveykova, V.I., Pote, J., 2020. Prevalence of beta-Lactam and sulfonamide resistance genes in a freshwater reservoir, Lake Bret, Switzerland. Expo. Health 12 (2), 187–197. https://doi.org/10.1007/s12403-019-00304-0.

Larsson, D.G.J., Flach, C.F., 2022. Antibiotic resistance in the environment. Nat. Rev. Microbiol. 20 (5), 257–269. https://doi.org/10.1038/s41579-021-00649-x.

Laursen, L., 2018. A call for early-career scientists to build a global science accord. Nature 562, S64. https://doi.org/10.1038/d41586-018-06973-2.

Li, L.G., Huang, Q., Yin, X.L., Zhang, T., 2020. Source tracking of antibiotic resistance genes in the environment - challenges, progress, and prospects. Water Res. 185, 116127 https://doi.org/10.1016/j.watres.2020.116127.

Li, X., Cheng, G.D., Wang, L.X., Wang, J.L., Ran, Y.H., Che, T., Li, G.Q., He, H.L., Zhang, Q., Jiang, X.Y., Zou, Z.M., Zhao, G.F., 2021. Boosting geoscience data sharing in China. Nat. Geosci. 14 (8), 541–542. https://doi.org/10.1038/s41561-021-00808-y.

Löffler, D., Römbke, J., Meller, M., Ternes, T.A., 2005. Environmental fate of pharmaceuticals in water/sediment systems. Environ. Sci. Technol. 39 (14), 5209–5218. https://doi.org/10.1021/es0484146.

Marti, E., Variatza, E., Balcazar, J.L., 2014. The role of aquatic ecosystems as reservoirs of antibiotic resistance. Trends Microbiol. 22 (1), 36–41. https://doi.org/10.1016/j.tim.2013.11.001.

Martínez, J.L., 2008. Antibiotics and antibiotic resistance genes in natural environments. Science 321 (5887), 365–367. https://doi.org/10.1126/science.1159483.

Martinez, J.L., Coque, T.M., Baquero, F., 2015. What is a resistance gene? Ranking risk in resistomes. Nat. Rev. Microbiol. 13 (2), 116–123. https://doi.org/10.1038/nrmicro3399.

Martiny, J.B.H., Bohannan, B.J.M., Brown, J.H., Colwell, R.K., Fuhrman, J.A., Green, J. L., Horner-Devine, M.C., Kane, M., Krumins, J.A., Kuske, C.R., Morin, P.J., Naeem, S., Ovreas, L., Reysenbach, A.L., Smith, V.H., Staley, J.T., 2006. Microbial biogeography: putting microorganisms on the map. Nat. Rev. Microbiol. 4 (2), 102–112. https://doi.org/10.1038/nrmicro1341.

Nadimpalli, M.L., Marks, S.J., Montealegre, M.C., Gilman, R.H., Pajuelo, M.J., Saito, M., Tsukayama, P., Njenga, S.M., Kiiru, J., Swarthout, J., Islam, M.A., Julian, T.R., Pickering, A.J., 2020. Urban informal settlements as hotspots of antimicrobial resistance and the need to curb environmental transmission. Nat. Microbiol. 5 (6), 787–795. https://doi.org/10.1038/s41564-020-0722-0.

Okeke, I.N., Edelman, R., 2001. Dissemination of antibiotic-resistant bacteria across geographic borders. Clin. Infect. Dis. 33 (3), 364–369. https://doi.org/10.1086/321877.

Ostman, M., Lindberg, R.H., Fick, J., Bjorn, E., Tysklind, M., 2017. Screening of biocides, metals and antibiotics in Swedish sewage sludge and wastewater. Water Res. 115, 318–328. https://doi.org/10.1016/j.watres.2017.03.011.

Pehrsson, E.C., Tsukayama, P., Patel, S., Mejia-Bautista, M., Sosa-Soto, G., Navarrete, K. M., Calderon, M., Cabrera, L., Hoyos-Arango, W., Bertoli, M.T., Berg, D.E., Gilman, R.H., Dantas, G., 2016. Interconnected microbiomes and resistomes in low-income human habitats. Nature 533 (7602), 212–216. https://doi.org/10.1038/nature17672.

Pei, R., Kim, S.C., Carlson, K.H., Pruden, A., 2006. Effect of river landscape on the sediment concentrations of antibiotics and corresponding antibiotic resistance genes (ARG). Water Res. 40 (12), 2427–2435. https://doi.org/10.1016/j.watres.2006.04.017.

Prince, K.D., Taylor, S.D., Angelini, C., 2020. A global, cross-system meta-analysis of polychlorinated biphenyl biomagnification. Environ. Sci. Technol. 54 (18), 10989–11001. https://doi.org/10.1021/acs.est.9b07693.

Rodriguez-Mozaz, S., Chamorro, S., Marti, E., Huerta, B., Gros, M., Sanchez-Melsio, A., Borrego, C.M., Barcelo, D., Balcazar, J.L., 2015. Occurrence of antibiotics and antibiotic resistance genes in hospital and urban wastewaters and their impact on the receiving river. Water Res. 69, 234–242. https://doi.org/10.1016/j.watres.2014.11.021.

Schar, D., Zhao, C., Wang, Y., Larsson, D.G.J., Gilbert, M., Van Boeckel, T.P., 2021. Twenty-year trends in antimicrobial resistance from aquaculture and fisheries in Asia. Nat. Commun. 12 (1), 5384. https://doi.org/10.1038/s41467-021-25655-8.

Shin, J., Rhee, C., Shin, J., Jang, H.M., Shin, S.G., Kim, Y.M., 2020. Determining the composition of bacterial community and relative abundance of specific antibiotics resistance genes via thermophilic anaerobic digestion of sewage sludge. Bioresour. Technol. 311, 123510 https://doi.org/10.1016/j.biortech.2020.123510.

Soundharajan, B.S., Adeloye, A.J., Remesan, R., 2016. Evaluating the variability in surface water reservoir planning characteristics during climate change impacts assessment. J. Hydrol. 538, 625–639. https://doi.org/10.1016/j.jhydrol.2016.04.051.

Su, J.Q., Wei, B., Ou-Yang, W.Y., Huang, F.Y., Zhao, Y., Xu, H.J., Zhu, Y.G., 2015. Antibiotic resistome and its association with bacterial communities during sewage sludge composting. Environ. Sci. Technol. 49 (12), 7356–7363. https://doi.org/10.1021/acs.est.5b01012.

Subirats, J., Timoner, X., Sanchez-Melsio, A., Balcazar, J.L., Acuna, V., Sabater, S., Borrego, C.M., 2018. Emerging contaminants and nutrients synergistically affect the spread of class 1 integron-integrase (intI1) and sul1 genes within stable streambed bacterial communities. Water Res. 138, 77–85. https://doi.org/10.1016/j.watres.2018.03.025.

Suda, K.J., Hicks, L.A., Roberts, R.M., Hunkler, R.J., Taylor, T.H., 2014. Trends and seasonal variation in outpatient antibiotic prescription rates in the United States, 2006 to 2010. Antimicrob. Agents Chemother. 58 (5), 2763–2766. https://doi.org/10.1128/AAC.02239-13.

Tedersoo, L., Kungas, R., Oras, E., Koster, K., Eenmaa, H., Leijen, A., Pedaste, M., Raju, M., Astapova, A., Lukner, H., Kogermann, K., Sepp, T., 2021. Data sharing practices and data availability upon request differ across scientific disciplines. Sci. Data 8 (1), 192. https://doi.org/10.1038/s41597-021-00981-0.

Tuomanen, E., Cozens, R., Tosch, W., Zak, O., Tomasz, A., 1986. The rate of killing of Escherichia coli by β-lactam antibiotics is strictly proportional to the rate of bacterial growth. Microbiology 132, 1297–1304. https://doi.org/10.1016/j.watres.2012.09.051.

United Nations, 2015. Transforming our World: The 2030 Agenda for Sustainable Development.

Van Boeckel, T.P., Brower, C., Gilbert, M., Grenfell, B.T., Levin, S.A., Robinson, T.P., Teillant, A., Laxminarayan, R., 2015. Global trends in antimicrobial use in food animals. Proc. Natl. Acad. Sci. U.S.A. 112 (18), 5454–5649. https://doi.org/10.1073/pnas.1503141112.

Van Boeckel, T.P., Gandra, S., Ashok, A., Caudron, Q., Grenfell, B.T., Levin, S.A., Laxminarayan, R., 2014. Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data. Lancet Infect. Dis. 14 (8), 742–750. https://doi.org/10.1016/s1473-3099(14)70780-7.

Vikesland, P.J., Pruden, A., Alvarez, P.J.J., Aga, D., Burgmann, H., Li, X.D., Manaia, C. M., Nambi, I., Wigginton, K., Zhang, T., Zhu, Y.G., 2017. Toward a comprehensive strategy to mitigate dissemination of environmental sources of antibiotic resistance. Environ. Sci. Technol. 51 (22), 13061–13069. https://doi.org/10.1021/acs.est.7b03623.

Wang, J.F., Li, X.H., Christakos, G., Liao, Y.L., Zhang, T., Gu, X.D., Zheng, X.Y., 2010. Geographical detectors-based health risk assessment and its application in the neural tube defects study of the Heshun region. China. Int. J. Geogr. Inf. Sci. 24 (1), 107–127. https://doi.org/10.1080/13658810802443457.

WHO, 2015. Global Action Plan on Antimicrobial Resistance. World Health Organization, Geneva.

Wilkinson, J.L., Boxall, A.B.A., Kolpin, D.W., Leung, K.M.Y., Lai, R.W.S., Galban-Malagon, C., et al., 2022. Pharmaceutical pollution of the world's rivers. Proc. Natl. Acad. Sci. U. S. A. 119 (8), e2113947119 https://doi.org/10.1073/pnas.2113947119.

Yang, Y.Y., Song, W.J., Lin, H., Wang, W.B., Du, L.N., Xing, W., 2018. Antibiotics and antibiotic resistance genes in global lakes: a review and meta-analysis. Environ. Int. 116, 60–73. https://doi.org/10.1016/j.envint.2018.04.011.

Zainab, S.M., Junaid, M., Xu, N., Malik, R.N., 2020. Antibiotics and antibiotic resistant genes (ARGs) in groundwater: a global review on dissemination, sources, interactions, environmental and human health risks. Water Res. 187, 116455 https://doi.org/10.1016/j.watres.2020.116455.

Zhang, X.X., Brandt, M., Tong, X.W., Ciais, P., Yue, Y.M., Xiao, X.M., Zhang, W.M., Wang, K., Fensholt, R., 2022. A large but transient carbon sink from urbanization and rural depopulation in China. Nat. Sustain. 5 (4), 321–328. https://doi.org/10.1038/s41893-021-00843-y.

Zhang, Z.Y., Zhang, Q., Wang, T.Z., Xu, N.H., Lu, T., Hong, W.J., Penuelas, J., Gillings, M., Wang, M.X., Gao, W.W., Qian, H.F., 2022. Assessment of global health risk of antibiotic resistance genes. Nat. Commun. 13 (1), 1553. https://doi.org/10.1038/s41467-022-29283-8.

Zhao, Y., Yang, Q.E., Zhou, X., Wang, F.H., Muurinen, J., Virta, M.P., Brandt, K.K., Zhu, Y.G., 2020. Antibiotic resistome in the livestock and aquaculture industries: status and solutions. Crit. Rev. Environ. Sci. Technol. 51 (19), 2159–2196. https://doi.org/10.1080/10643389.2020.1777815.

Zhu, Y.G., Gillings, M., Simonet, P., Stekel, D., Banwart, S., Penuelas, J., 2018. Human dissemination of genes and microorganisms in Earth's Critical Zone. Glob. Chang. Biol. 24 (4), 1488–1499. https://doi.org/10.1111/gcb.14003.

Zhu, Y.G., Johnson, T.A., Su, J.Q., Qiao, M., Guo, G.X., Stedtfeld, R.D., Hashsham, S.A., Tiedje, J.M., 2013. Diverse and abundant antibiotic resistance genes in Chinese swine farms. Proc. Natl. Acad. Sci. U. S. A. 110 (9), 3435–3440. https://doi.org/10.1073/pnas.1222743110.

Zhu, Y.G., Zhao, Y., Li, B., Huang, C.L., Zhang, S.Y., Yu, S., Chen, Y.S., Zhang, T., Gillings, M.R., Su, J.Q., 2017. Continental-scale pollution of estuaries with antibiotic resistance genes. Nat. Microbiol. 2, 16270. https://doi.org/10.1038/nmicrobiol.2016.270.

Zhu, Y.G., Zhao, Y., Zhu, D., Gillings, M., Penuelas, J., Ok, Y.S., Capon, A., Banwart, S., 2019. Soil biota, antimicrobial resistance and planetary health. Environ. Int. 131, 105059 https://doi.org/10.1016/j.envint.2019.105059.