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Review

A systematic review of antibiotics and antibiotic resistance genes in estuarine and coastal environments

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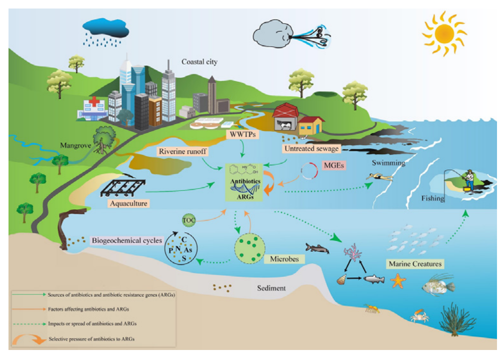
HIGHLIGHTS

- Antibiotics distribution is driven by antibiotic usage and environmental variables.
- Latitudinal variations of ARGs link with environmental variables and MGEs.
- ARGs distribution exhibits distance decay law at continental and global scale.
- Antibiotics and ARGs interfere element cycling via inhibiting functional bacteria.
- Antibiotics and ARGs pose potential health threats to marine organisms and humans.

GRAPHICAL ABSTRACT



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ABSTRACT

Antibiotics and antibiotic resistance genes (ARGs) are prevalent in estuarine and coastal environments due to substantial terrestrial input, aquaculture effluent, and sewage discharge. In this article, based on peer-reviewed papers, the sources, spatial patterns, driving factors, and environmental implications of antibiotics and ARGs in global estuarine and coastal environments are discussed. Riverine runoff, WWTPs, sewage discharge, and aquaculture, are responsible for the prevalence of antibiotics and ARGs. Geographically, pollution due to antibiotics in low- and middle-income countries is higher than that in high-income countries, and ARGs show remarkable latitudinal variations. The distribution of antibiotics is driven by antibiotic usage and environmental variables (heavy metals, nutrients, organic pollutants, etc.), while ARGs are affected by antibiotics residues, environmental variables, microbial communities, and mobile genetic elements (MGEs). Antibiotics and ARGs alter microbial communities and biogeochemical cycles, as well as pose threats to marine organisms and human health. Our results provide comprehensive insights into the transport and environmental behaviors of antibiotics and ARGs in global estuarine and coastal environments.

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1. Introduction

Antibiotics have attracted global concerns due to their profound environmental effects (Galera-Laporta and Garcia-Ojalvo, 2020; Hamid et al., 2018; Reverter et al., 2020; Sun et al., 2020a), large amounts of anthropogenic emissions (Pärnänen et al., 2019; Van Boeckel et al., 2014), as well as ubiquitous occurrence in various environments (Rodriguez-Mozaz et al., 2015; Tolentino et al., 2019; Zhu et al., 2017). Since penicillin was discovered in 1929 (Fleming, 1929), antibiotics have been widely applied for human and livestock uses (Versporten et al., 2014). A recent study projected that global antibiotics consumption in 2030 might be as much as 200% higher than the level in 2015, under the scenario of no policy interferences (Klein et al., 2018). Substantial anthropogenic antibiotic residues result in serious environmental problems. For instance, thiamphenicol is demonstrated to inhibit nitrate reduction processes and stimulate greenhouse gas N_2O release (Yin et al., 2016). Antibiotic exposure to newborn is closely linked with the slow growth of child during the first six years of life, owing to the disturbed microbial colonization in intestinal tract (Uzan-Yulzari et al., 2021). Besides, wide usage of antibiotics poses selective pressure on microorganisms, thus resulting in antibiotic resistance genes (ARGs) enrichment (Andersson and Hughes, 2014; Migliorini et al., 2019; Wang et al., 2019).

ARGs render antibiotics useless mainly through cellular protection, efflux pumps, enzymatic destruction, target protection as well as antibiotic deactivation (Chen et al., 2019; Pruden et al., 2006; Wilson et al., 2020; Zhang et al., 2019). They can disable the efficacy of antibiotics against pathogens so that infection is not effectively inhibited in clinical treatment (Pärnänen et al., 2019; Ward et al., 2014). Moreover, owing to the horizontal gene transfer (HGT) of mobile genetic elements (MGEs), such as integrons, transposons, and plasmids, ARGs are becoming increasingly prevalent in the environment (Pallares-Vega et al., 2019; Wang et al., 2016; Wang et al., 2018; Zhao et al., 2019a).

Previously, antibiotics and ARGs have been frequently reported in rivers (Chen and Zhou, 2014; Rodriguez-Mozaz et al., 2015), lakes (Li et al., 2012a; Tang et al., 2015), groundwater (Liu et al., 2019; Szekeres et al., 2018; Tong et al., 2020), and estuarine and coastal environments (Griffin et al., 2019; Zhu et al., 2017). Antibiotics and ARGs in lakes (Yang et al., 2018), rivers (Singh et al., 2019), and groundwater (Zainab et al., 2020) were systematically summarized. However, studies on antibiotics or ARGs in estuarine and coastal environments are still scattered and in lack of an inclusive review. Estuarine and coastal environments are unique regions where land and ocean, freshwater and saltwater interconnect (Ward et al., 2020). Owing to the unique geographical location, estuarine and coastal environments provide essential ecosystem services (Barbier et al., 2011; Duarte et al., 2013; Shields et al., 2017). However, as a consequence of antibiotics and ARGs, biogeochemical cycling, ecological security, and human health are facing unprecedented challenges in estuarine and coastal environments (Hou et al., 2015; Leonard et al., 2015; Zhao et al., 2019b). A systematic review integrating previous literature would provide comprehensive understandings to mitigate antibiotics and ARGs pollution in this region.

Here, a comprehensive review on antibiotics and ARGs in global estuarine and coastal environments is conducted. The main objectives of this review are (1) to summarize their major discharge sources, (2) to explore their geographical patterns at a global scale, (3) to discuss their relationships with environmental variables, anthropogenic activities, MGEs, and microbial communities, and (4) to review their environmental implications.

2. Methodology

This review was conducted following the guideline of preferred items for reporting systematic reviews and meta-analyses (PRISMA) (Moher et al., 2009; Gurevitch et al., 2018; Zainab et al., 2020) (Fig. 1) through online databases. Literature databases involved Google Scholar, Web of Science, Science Director, and Springer. Key words for searching literatures were as follows: "antibiotics", "antimicrobial", "antibiotic resistance gene", "antimicrobial resistance", "ARGs", "ocean", "sea", "Bay", "estuary", "marine", "coastal", as well as "Gulf" (including singular and plural forms of these words). All the collected studies were published online from January 1, 2007 to January 1, 2020.

The PRISMA method produced a total of 2078 studies from the online databases and 34 studies from other sources. After removal of 1052 duplicates, 1060 studies were left. Filtered by reading title and abstract, studies unavailable on antibiotics and ARGs or other study areas were excluded, and 299 studies remained. Full-text assessment was performed to exclude the studies regarding terrestrial coast, conference abstract, and overlapping studies. Ultimately, 202 and 145 records (Fig. 3a) were selected to conducted qualitative and quantitative synthesis, respectively. Regarding quantitative synthesis, only samples from surface sediment (top 0–10 cm) and surface water (top 100 cm) were included. In view of data comparability, records on ARGs only available on the copy numbers of ARGs and 16S rRNA were considered. Absolute abundance of genes in these articles was converted to relative abundance by the method of Yang et al. (2018). In brief, absolute abundance of ARGs was normalized by the absolute abundance of 16S rRNA, and the unit of ARGs abundance is copies/16S rRNA. Besides, we recalculated the average values in all the literatures to avoid statistical bias, as zeros were excluded to calculate the average value in some original literatures.

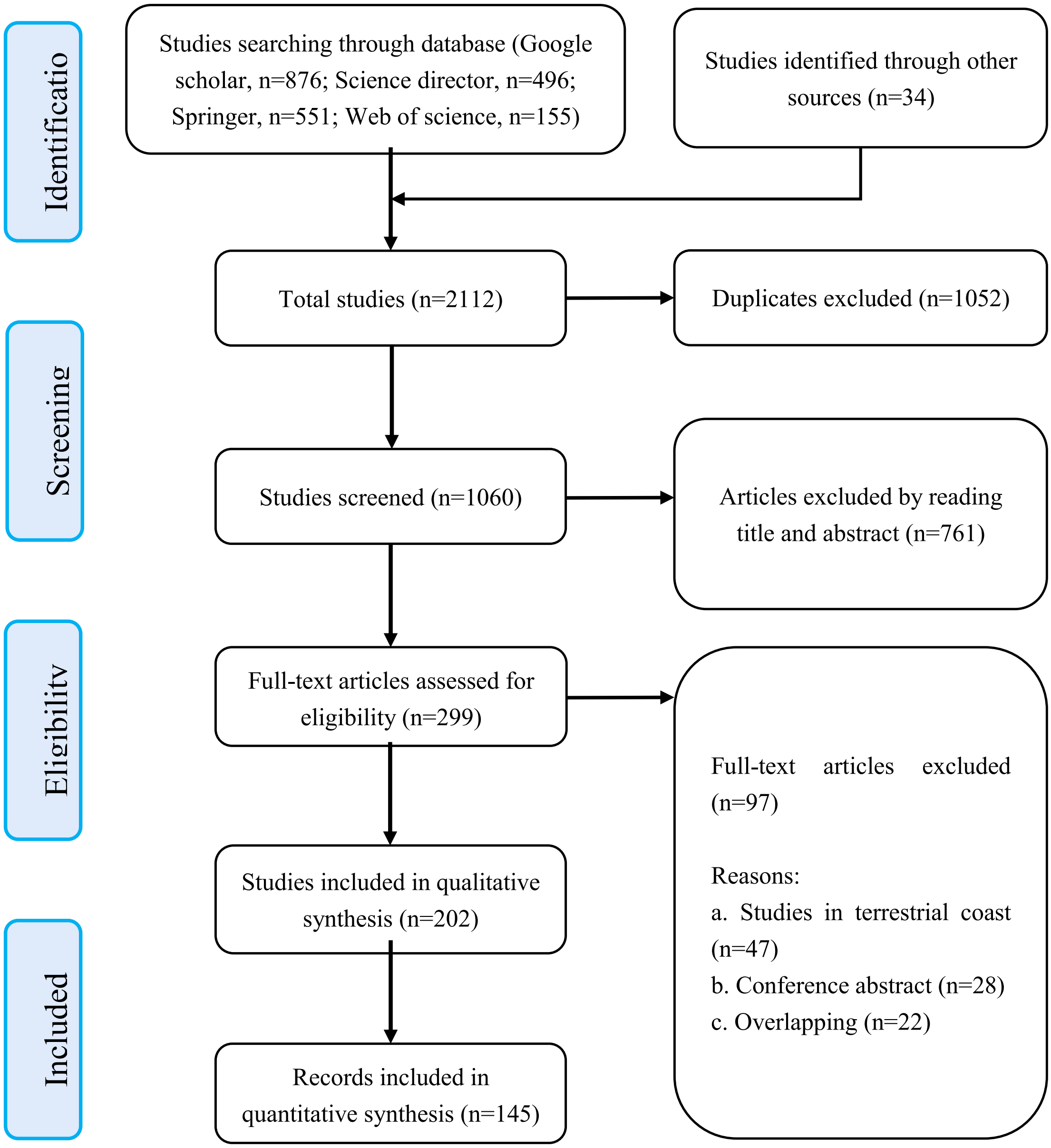

Fig. 1. Framework of reporting systematic reviews and meta-analyses (PRISMA) performed in this study.

A total of 145 quantitative records of antibiotics and ARGs in estuarine and coastal environments were collected (Fig. 2A), most of which were from Europe (Fig. 2B) and East Asia (Fig. 2C). There were 80 and 25 records of antibiotics in estuarine and coastal water and sediment, respectively (Fig. 2D). Related information on study sites, antibiotic concentrations, pollution sources, correlated variables, environmental implications, and authors are shown in Tables S1 and S2. Regarding ARGs, 23 and 17 records in estuarine and coastal water and sediment were collected, respectively (Fig. 2D). Related information on the study sites, ARG abundances, pollution sources, correlated variables, environmental implications, and associated authors are summarized in Table S3. Sulfonamides, fluoroquinolones, tetracyclines, macrolides, and their resistance genes were the major antibiotics and ARGs. The abbreviation of reviewed antibiotics was summarized in Table S4.

Distance decay analysis was conducted based on Spearman's rank correlation between geographical distance and the similarity of antibiotics or ARGs. The similarity was defined as the ratio of antibiotic concentrations or ARG abundances between the two sites. The larger value was treated as the denominator, and the smaller value was the numerator. The defined similarity ranged from 0 (low similarity) to 1 (high similarity). Distance decay was considered to be significant only when Spearman's rank correlation coefficient was below zero and p-value was inferior to 0.05. Distance decay analysis on global scale was conducted using all the record across the world, while on continental scale was carried out using data within one single continent. Mann-Whitney *U* test was used to test the difference of antibiotics concentrations between high- income and low- and middle-income countries ($p < 0.05$ indicating significance). Records from each study were treated as a single data point to perform Mann-Whitney *U* test using SPSS 25.0. Latitudinal pattern of ARGs was identified using polynomial fitting, where p-value was applied to test the significance. p-Value <0.05 indicates a significant polynomial fitting. ArcGIS 10.2 was used to map the distribution of study areas that reported antibiotics and ARGs in global estuarine and coastal environments. Origin 2020 was employed to draw Venn diagrams, scatter plots, cluster heatmaps, and box plots, based on the average abundance of each record. Gephi 9.1 was applied to draw a co-occurrence network between antibiotics and environmental variables using Spearman's rank correlation coefficient, and missing data were processed by excluding cases pairwise using SPSS 25.0. Excluding cases pairwise makes it possible to identify remarkable

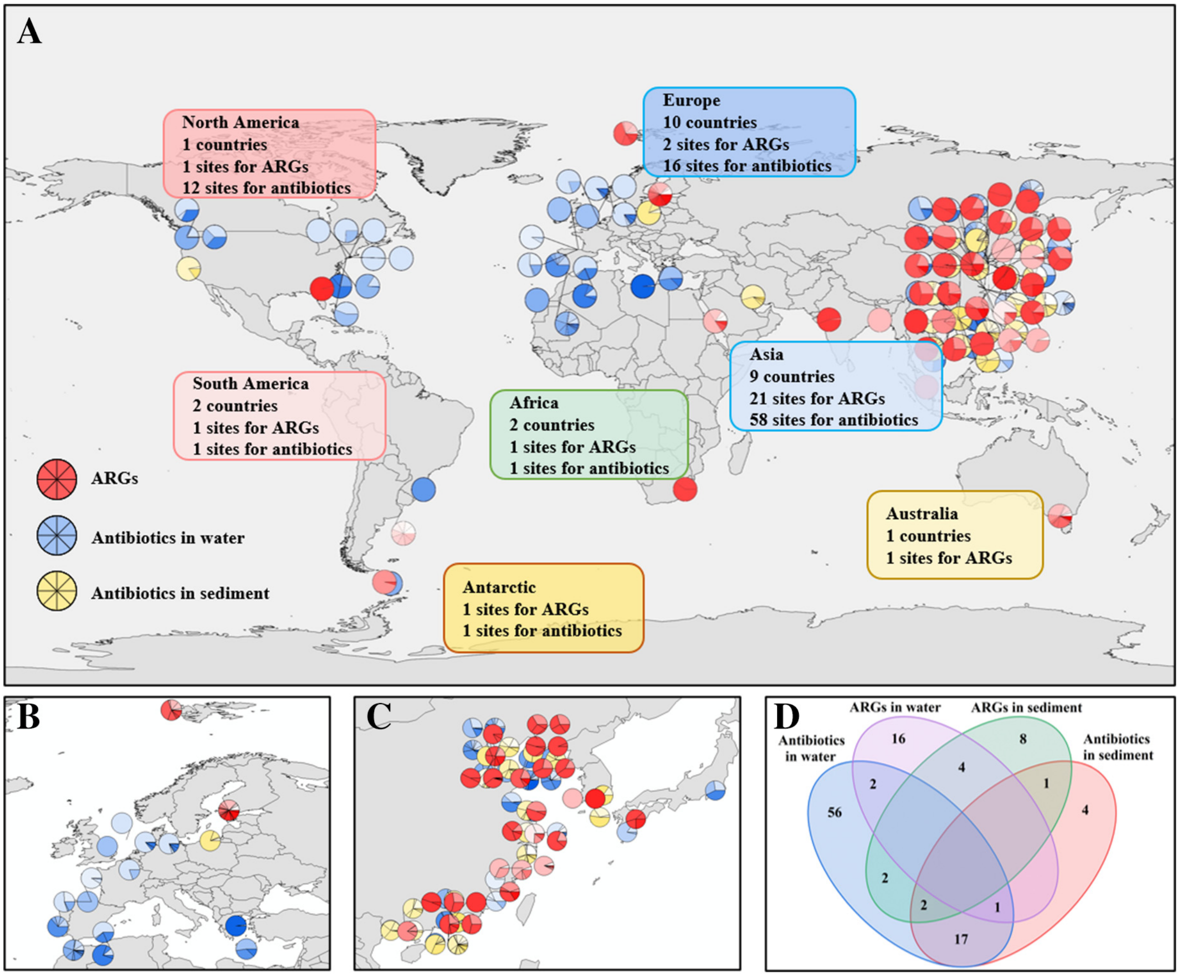

Fig. 2. Geographical distributions of antibiotics and ARGs in estuarine and coastal environments of the world (A), Europe (B), and East Asia (C). The number and composition of reported sites on antibiotics or ARGs according to previous studies (D).

correlations that was scattered in different studies, despite the existence of missing values.

3. Sources of antibiotics and ARGs

Riverine runoff, WWTPs, sewage discharge, and aquaculture were major pollution sources of antibiotics and ARGs in estuarine and coastal environments (Table 1, Fig. 3, Tables S1–S3; Table 1 was summarized via the references in Tables S1–S3). There are 33.75–55.00% of study sites identified riverine runoff as a source of antibiotics and ARGs (Table 1). Due to substantial antibiotic consumption in terrestrial areas, massive amounts of residual antibiotics and ARGs from both human and veterinary pathways flow into river systems, which are ultimately discharged into estuarine and coastal environments (Zhang et al., 2015a). It was estimated by Zhang et al. (2015a) that 92,700 tons of antibiotics were consumed in China annually; eventually, >58% of the antibiotics were discharged into 58 river basins of China. Once rivers flow into the ocean, the abundance of antibiotics and ARGs usually decreases due to seawater dilution. Many studies have revealed the downtrend of antibiotics and ARGs from upstream to downstream of estuaries. Xu et al. (2013) detected antibiotics in Pearl River Estuary water, and their results indicated that most targeted antibiotics, including SD, SMZ, SMX, NOR, OFL, CIP, ERY, and ROX, showed a downward trend in terms of their concentration towards the South China Sea. Lu et al. (2015) denoted terrestrial runoff input as the main ARG source of the Liaohe River Estuary; the upstream estuarine water had a higher abundance of sulfonamide resistance genes and *intI1* due to pollution from riverine runoff.

WWTPs were identified as a source of antibiotics and ARGs at 15.00–47.50% of reported sites (Table 1). WWTP effluent, with various antibiotics and ARGs, provides suitable conditions for the proliferation of antibiotic-resistant bacteria (ARB) and the HGT of MGEs (Griffin et al., 2020; Pazda et al., 2019; Su et al., 2020a; Zhang et al., 2020a). Most WWTPs fail to eliminate antibiotics and ARB effectively; hence, these are discharged into estuarine and coastal environments via WWTPs outlets (Pazda et al., 2019; Pärnänen et al., 2019). In Victoria Harbor, Hong Kong, China, 14.4 kg of targeted antibiotics were estimated to be discharged per day into seawater through the effluents of WWTPs, which is even higher than the flux from the Pearl River (Minh et al., 2009). In Athens, Greece, 127.8 ng/L of AMX was detected in the seawater of the Inner Saronic Gulf, where anthropogenic inputs were absent but the second-largest WWTP of Europe is located (Alygizakis et al., 2016). Prevalence of antibiotics and ARB in WWTPs provides an opportunity to estimate antibiotic consumption and antibiotic resistance in the human body. Pärnänen et al. (2019) performed such work and provided a novel insight into the antibiotic resistance in a clinical environment.

Coastal sewage discharge has also been recognized as an important source of antibiotics and ARGs at 20.00–48.00% of reported sites (Table 1), particularly in low- and middle-income countries. High-, middle-, and low-income countries were classified based on the World Bank Report (2018). In these countries, poorly treated or untreated wastewater is directly discharged into the ocean, which triggers the widespread occurrence of antibiotics and ARGs in estuarine and coastal environments (Qiao et al., 2018). For example, a study by

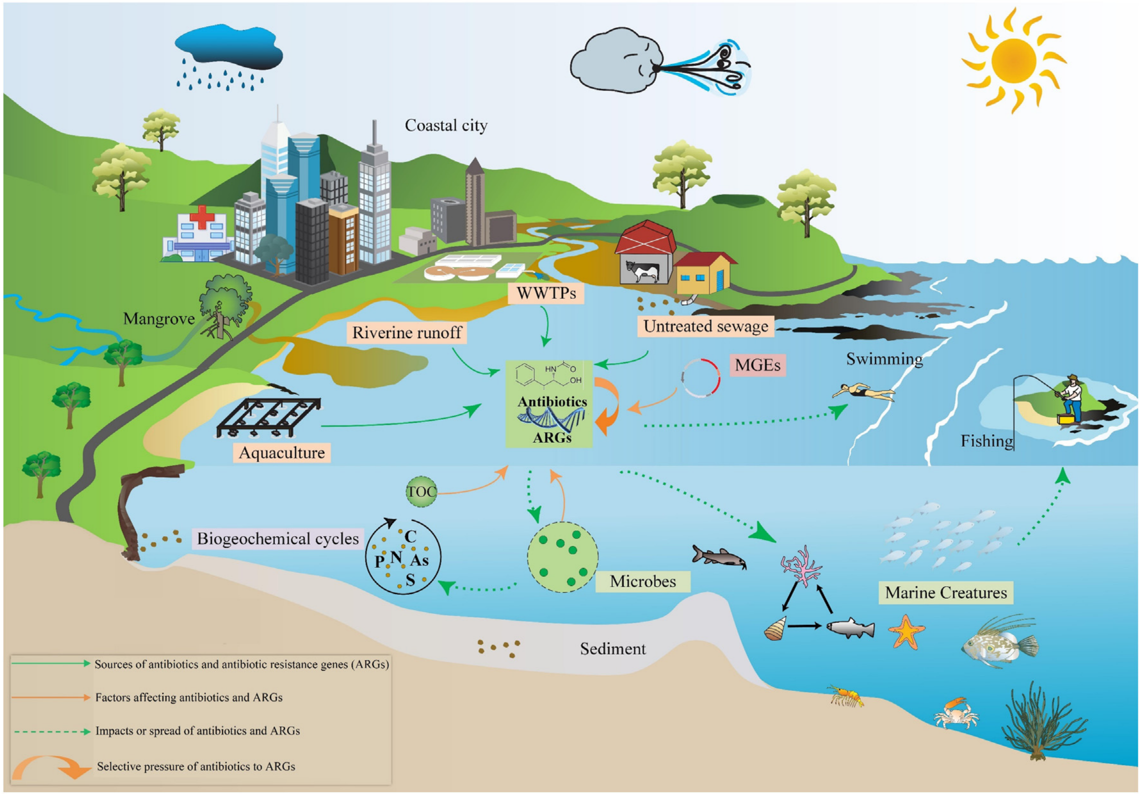

Fig. 3. The transport of antibiotics and ARGs in estuarine and coastal environments. Riverine runoff, coastal WWTPs, aquaculture effluent and sewage discharge were main sources of antibiotics and ARGs. The abundances of antibiotics and ARGs were affected by environmental variables. The abundances of ARGs were also driven by MGEs and microbes. Antibiotics posed a selective pressure on microbes and enriched ARGs. Antibiotics and ARGs disturbed biogeochemical cycles via affecting microbial community. Besides, antibiotics and ARGs posed health threat on marine creatures. Antibiotics and ARGs can be transferred into human body through direct (e.g. swimming and fishing) or indirect contact (e.g. dietary intake).

Ali et al. (2017) in the coastal seawater of the Red Sea suggested that the maximum concentration of PPCPs, including TMP and SMX, was found in seawater close to the sewage outlet of Al-Arbaeen Lagoon. Due to the limited capacity of WWTPs, extensive untreated sewage was directly discharged into the coastal water in Al-Arbaeen Lagoon (Ali et al., 2017). Similarly, >1 × 10^5 m^3 per day of untreated sewage water from both industrial and domestic activities was discharged into the Cochin Estuary, India (Divya and Hatha, 2019; Gupta et al., 2016), thus allowing resistance genes against ampicillin and tetracycline to be prevalent in *E. coli* (Divya and Hatha, 2019).

Table 1
Pollution sources of antibiotics and ARGs in coastal environment identified in reported sites. This table was summarized via Tables S1–S3. Reported counts denoted the number of times for certain pollution sources identified in previous literatures. Proportion of total reported sites was calculated through normalizing reported counts to the number of study sites.

Pollutants and environments	Identified pollution sources	Reported counts	Proportion of total reported sites
Antibiotics in estuarine and coastal water	Riverine runoff	27	33.75%
	WWTPs	38	47.50%
	Sewage discharge	37	46.25%
	Aquaculture	12	15.00%
	Other sources	7	8.75%
Antibiotics in estuarine and coastal sediment	Riverine runoff	12	48.00%
	WWTPs	9	36.00%
	Sewage discharge	12	48.00%
	Aquaculture	10	40.00%
	Other sources	0	0.00%
ARGs in estuarine and coastal environments	Riverine runoff	22	55.00%
	WWTPs	6	15.00%
	Sewage discharge	8	20.00%
	Aquaculture	11	27.50%
	Other sources	4	5.00%

Furthermore, aquaculture effluent has been regarded as an important source of antibiotics and ARGs at 15.00–40.00% of study sites (Table 1). Aquaculture industry has developed in the coastal regions because of the suitable aquatic environment and the dietary habits of residents living in these regions (Froehlich et al., 2018). For preventing pathogenic infections or for therapeutic treatment against such infections, antibiotics are commonly added in fishery feed (Liu et al., 2017). As a result, high concentrations of antibiotic residues were widely detected in the nearby environments of aquaculture grounds. For instance, pharmaceuticals, including fluoroquinolones, sulfonamides, and macrolides, were detected at an average concentration of 195 ng/g in the sediment of a coastal fish farm in Korea, which was 40% higher than that in nearby coastal areas (Kim et al., 2017). Additionally, a comprehensive investigation to aquaculture areas along the entire China's coast revealed that sulfonamide resistance genes, especially *sul1* and *sul2*, were the most prevalent ARGs in sediment, as sulfonamides were among the most common antibiotics used in aquaculture (Gao et al., 2018).

4. Geographical distribution in global estuarine and coastal environments

4.1. Global geographical pattern of antibiotics and ARGs

The distribution of antibiotics and ARGs was highly heterogeneous on the global scale. The heatmap of antibiotics indicated that the antibiotic concentrations of high-income countries were remarkably lower than those of low- and middle-income countries in both water (Fig. 4A, Mann-Whitney *U*, $p < 0.00$) and sediment (Fig. 4B, Mann-Whitney *U*, $p < 0.00$). The global antibiotic consumption was found to have increased by 36% from 2000 to 2010 (Van Boeckel et al., 2014) and by 65% in 2015 (Klein et al., 2018), most of which was contributed by low- and middle-income countries (Högberg et al., 2014; Klein et al., 2018; Van Boeckel et al., 2014; Versporten et al., 2014). The large amount of antibiotic consumption along with poor sewage treatment facilities allowed for a greater prevalence of antibiotics in estuarine and coastal environments in low- and middle-income countries (Divya and Hatha, 2019; Gupta et al., 2016). Conversely, the ARG abundances of these countries were not remarkably higher than those of high-income countries (Fig. 4C, Mann-Whitney *U*, $p > 0.05$).

The distribution of ARG abundances showed obvious latitudinal gradients. The relative abundances of resistance genes against sulfonamides (Fig. 5A, $R^2 = 0.356$, $p = 0.000$) and β-lactams (Fig. 5B, $R^2 = 0.373$, $p = 0.006$) peaked at intermediate latitudes and declined towards both high and low latitudes. Tetracycline resistance genes increased with latitude (Fig. 5C, $R^2 = 0.160$, $p = 0.002$), while resistance genes against fluoroquinolones (Fig. 5D, $R^2 = 0.245$, $p = 0.023$), macrolide, lincosamide and streptogramin (Fig. 5E, $R^2 = 0.254$, $p = 0.039$), and aminoglycosides (Fig. 5F, $R^2 = 0.703$, $p = 0.001$) decreased with latitude. Genes encoding resistance to multiple drugs (Fig. S1B) and vancomycin (Fig. S1B) did not have a significant latitudinal variation but showed a clear increasing trend with latitude.

While the mechanisms behind the latitudinal variations of ARGs are largely unclear and likely multifaceted, some potential explanations are proposed. Temperature controls the growth of microbes carrying ARGs, thus likely inducing ARG abundance to show remarkable latitudinal gradient (Tourna et al., 2008). The discrepancy of optimal temperature for different ARBs (e.g. *E. coli* for 37 °C and *Acinetobacter* spp. for 33–35 °C) (Scheutz et al., 2005) would explain why different ARGs exhibited various latitude variation in this study. The link between temperature and antibiotic resistance have been demonstrated in American clinical setting, where higher temperature allowed more serious pathogen resistance to antibiotics in low latitudes (MacFadden et al., 2018). Similar results were also evidenced in influent water of WWTPs (Pärnänen

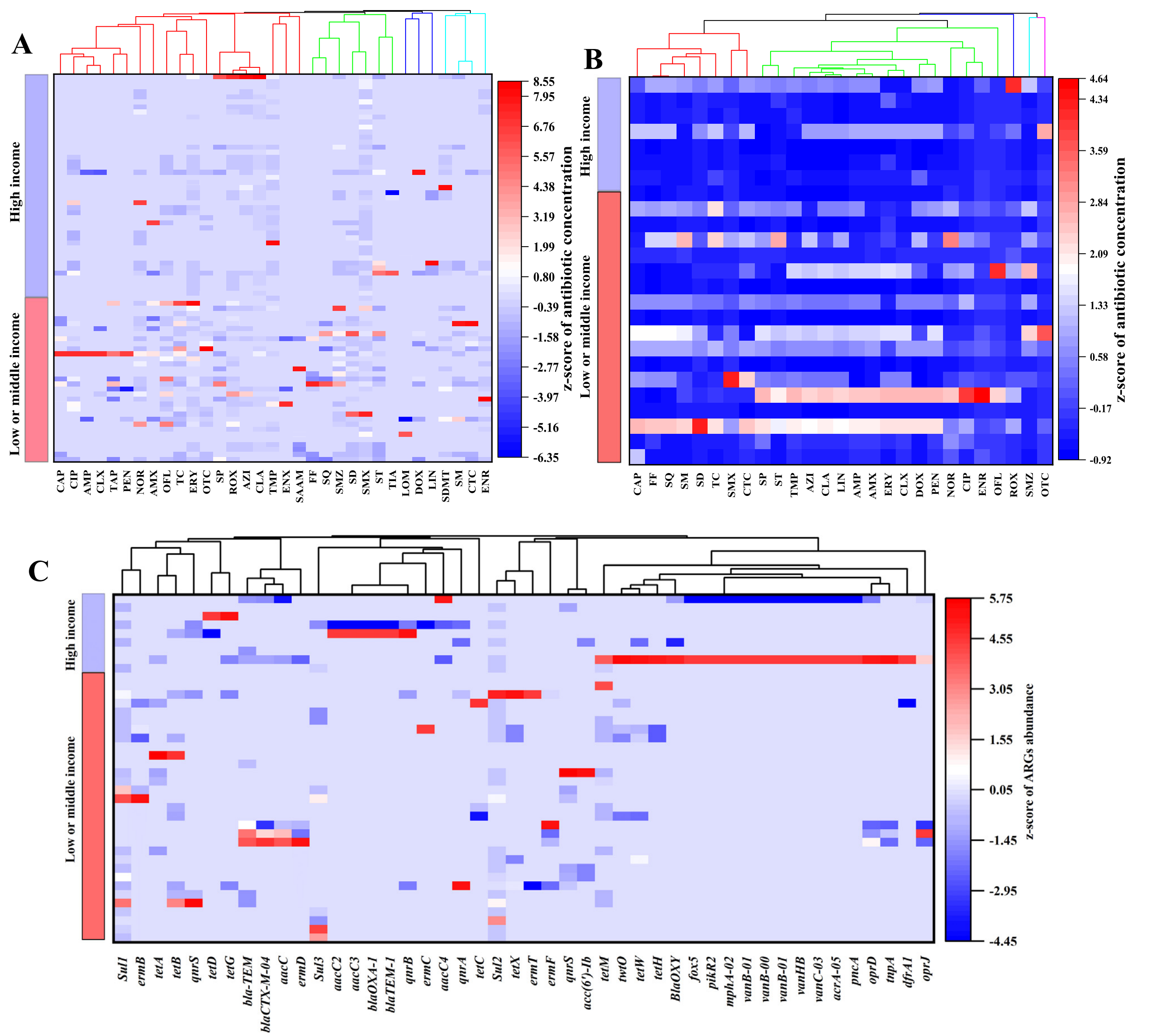

Fig. 4. Comparisons of antibiotics and ARGs between high-income countries and low- and middle-income countries. The clustering heatmaps of antibiotics in water (A) and sediment (B) showing the difference between high-income countries and low- and middle-income countries. The clustering heatmaps of ARGs (C) showing the difference between high-income countries and low- and middle-income countries.

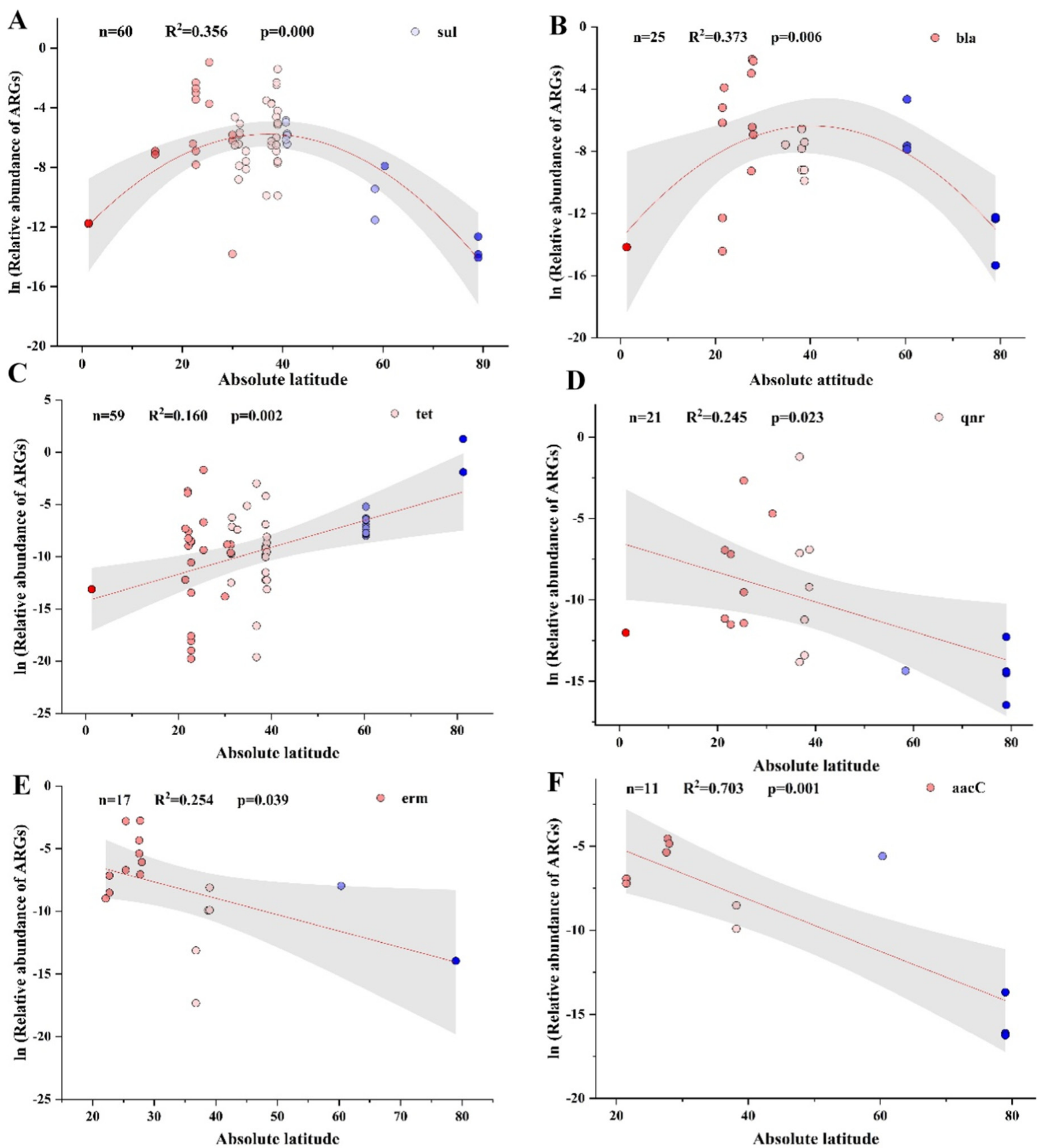

Fig. 5. Latitudinal variations of ARGs in global estuarine and coastal environments. Latitudinal variation of genes encoding resistance to sulfonamides (A), β-lactams (B), tetracyclines (C), fluoroquinolones (D), macrolide, lincosamide and streptogramin (E), and aminoglycosides (F). The color of each dot demotes absolute latitude. Absolute latitude increases from red to blue. Dash red line with grey hull is 95% confidence interval.

et al., 2019), activated sludge (Zhang et al., 2015b), manure (Lin et al., 2017; Sun et al., 2016), and forest soil (Bahram et al., 2018; Dunivin and Shade, 2018). Apart from temperature, some environmental variables such as pH and carbon/nitrogen ratio possibly drive the latitude gradient of ARGs through regulating the growth of ARBs (Bahram et al., 2018). As an illustration, ARG abundance was observed to be positively correlated with the distance to equator in global surface forest soil, where pH and carbon/nitrogen ratio were linked to ARG abundance, bacterial richness and abundance, as well as fungal abundance and biomass (Bahram et al., 2018). Additionally, the latitude gradients of ARGs would be explained by MGEs that usually facilitate the prevalence of ARGs through HGT (Pallares-Vega et al., 2019; Wang et al., 2016). As an example, an inverse association between latitude and MGE diversity was observed in Chinese drinking water, in accord with that in the observed ARGs diversity (Han et al., 2020). Likewise, MGE diversity was reported to peak at middle latitude and to decline towards both high and low latitudes in Chinese cropland (Du et al., 2020), which was in line with the distribution of ARG diversity.

Spearman's correlation analysis between concentration similarity and geographic distance was conducted to examine whether antibiotics and ARGs followed the distance-decay law. This showed that the distributions of antibiotics were clustered neither on a global scale (Fig. S2A, $n = 2224$, $r = 0.048$, $p = 0.025$) nor on a continental scale (Fig. S2B, $n = 1029$, $r = -0.036$, $p = 0.250$) in estuarine and coastal waters. Similar results were also observed for antibiotics in estuarine and coastal sediment both on global (Fig. S2C, $n = 684$, $r = -0.016$, $p = 0.784$) and continental scales (Fig. S2D, $n = 663$, $r = 0.004$, $p = 0.924$). These results suggested that the geographical distributions of antibiotics in estuarine and coastal environments exhibited high spatial heterogeneity on a large scale.

Likewise, the distance-decay law was not significant for ARGs in estuarine and coastal waters on either the global scale (Fig. S3A, n = 80, r = −0.039, p = 0.729) or the continental scale (Fig. S3B, n = 60, r = −0.013, p = 0.423). Conversely, a remarkable distance-decay relationship was observed for the distribution of ARGs in estuarine and coastal sediments on a global scale (Fig. S3C, n = 370, r = −0.0238, p = 0.000) and a continental scale (Fig. S3D, n = 288, r = −0.293, p = 0.000). The different patterns between water and sediment indicated that the environmental medium was a key factor for the abundance of ARGs. The study of Liu et al. (2018a) showed the opposite result in inland water bodies on a national scale, where 8.93% of the spatial variation was explained solely by spatial distance. Therefore, the spatial pattern of ARGs in water varied according to spatial scales and environments. Furthermore, Zhu et al. (2017) conducted a distance-decay analysis of ARG similarity in China's estuarine sediment but their results (r = 0.062, p = 0.447) were different from the results for the global and continental scales, implying that geographical distribution of ARGs in estuarine and coastal environments is likely to be dramatically scale-dependent.

4.2. Fluoroquinolones and fluoroquinolone resistance genes

Fluoroquinolones were among the most prevalent antibiotics in global estuarine and coastal environments (Tables S1–S2). In coastal water, NOR showed the highest average concentration of 41.43 ng/L, ranging from 0 to 380.81 ng/L (Fig. 6a). The maximum average concentration of NOR was reported in the Gran Canaria Island, Spain, where seawater was highly polluted by aquaculture and WWTP effluents (Afonso-Olivares et al., 2013). ENX, CIP, OFL, and SARA also exhibited high concentration, with average value of 22.75, 14.67, 26.41, and 14.50 ng/L (Fig. 6a, b). High level of fluoroquinolones was frequently detected in densely populated coastal regions, such as the coastal water of Zhuhai City, China (Li et al., 2018a). Besides, 91.60 ng/g of NOR and 28.40 ng/g of CIP were averagely detected in the sediment of this region, owing to wastewater pollution discharged by 1.67×10^6 urban residents and riverine inputs from the Pearl River runoff (Li et al., 2018a).

Fluoroquinolone resistance genes, including *qnrA*, *qnrB*, *qnrD*, and *qnrS* were broadly observed in estuarine and coastal environments (Lu et al., 2019a; Lu et al., 2019b; Ng et al., 2018; Tan et al., 2018; Ullah et al., 2019; Zhang et al., 2018a). As the most abundant fluoroquinolone resistance gene, *qnrA* was detected with an average abundance of 9.22×10^{-2} copies/16S rRNA in coastal environments (Fig. 6c). Lu et al. (2019a, 2019b) found 6.86×10^{-2} copies/16S rRNA of *qnrA* in a recirculating aquaculture system, where microplastics enriched genes encoding resistance to fluoroquinolones (Lu et al., 2019a). In a coastal city nearby the Red Sea, a mean of 9.68×10^{-9} and 1.44×10^{-5} copies/16S rRNA of *qnrB* and *qnrS* were detected, respectively (Ullah et al., 2019). These ARGs were two orders of magnitude higher than those observed in pristine Arctic region, where 4.64×10^{-6} and 5.56×10^{-7} copies/16S rRNA of *qnrB* and *qnrS* were detected, respectively (Tan et al., 2018). Besides, 5.57×10^{-7} to 2.96×10^{-5} copies/16S rRNA of *qepA*, a plasmid-mediated ARG, was determined in Arctic sediment, suggesting that the contribution of human activities and MGEs to the prevalence of fluoroquinolone resistance genes (Tan et al., 2018).

4.3. Tetracyclines and tetracycline resistance genes

Tetracyclines were common antibiotics with wide-spectrum to inhibit bacteria in clinical and veterinary settings (Dai et al., 2020). Average 21. 84 ng/L of TC, 42.29 ng/L of OTC, 8.19 ng/L of DOX, and 6.09 ng/L of CTC were detected in estuarine and coastal water across the world (Fig. 6a). In global coastal sediment, average concentration of TC, OTC, DOX, and CTC reached 6.83, 27.5, 3.66, and 4.53 ng/g, respectively (Fig. 6b). The maximum concentration of OTC was determined in the Haling Bay, China, with an average concentration of 417 ng/L, ranging from 0 to 15,163 ng/L, due to serious antibiotic contamination from shrimp pond and untreated sewage discharge (Chen et al., 2015a). These values were one to four orders of magnitude greater than those in the Yangtze River Estuary (ranging from 0.52 to 14.00 ng/L) (Shi et al., 2014), Zhuhai coast (average 35.10 ng/L) (Li et al., 2018a), and Stockholm archipelago (between 0 and 8.90 ng/L) (Björlenius et al., 2018). In sediment of the Gulf of Gdańsk, the average concentrations of TC and OTC were 17.85 and 113.00 ng/g, respectively (Siedlewicz et al., 2018). The two tetracyclines exhibited pronounced connections with environmental variables, including pH, TOC, and suspended particulate matter, due to the impacts of these environmental variables on the sorption of sediment to antibiotics (Siedlewicz et al., 2018).

Elevated levels of tetracycline resistance genes were observed in global estuarine and coastal environments, *tetG*, *tetW*, and *tetX* in particular (Fig. 6c). The average abundance of the three ARGs was over 1.00×10^{-2} copies/16S rRNA (Fig. 6c). As high as 1.48×10^{-1} copies/16S rRNA of *tetD* was revealed in oyster beds located in the Altamaha River Estuary, USA (Barkovskii et al., 2010). The value was three orders of magnitude superior to those reported in the heavily contaminated Red Sea coast (6.66×10^{-4} copies/16S rRNA) (Ullah et al., 2019), highlighting an urgent need to control antibiotic usage in aquaculture. Besides, tetracycline resistance genes would be enriched by tetracyclines in global estuarine and coastal environments (Guo et al., 2018; Niu et al., 2016; Suzuki et al., 2019; Zhang et al., 2018a). The associations between tetracyclines and their resistance genes were demonstrated in the Uwa Sea (Suzuki et al., 2019), Yangtze River Estuary (Guo et al., 2018), and Bohai Bay (Niu et al., 2016; Zhang et al., 2018a). All these regions suffered from severe tetracycline pollution from riverine runoff, WWTPs, or aquaculture, thus posing a selective pressure to microorganism (Guo et al., 2018; Niu et al., 2016; Suzuki et al., 2019; Zhang et al., 2018a).

4.4. Sulfonamides and sulfonamide resistance genes

The average concentration of SD, SP, SMX, and TMP reached 9.10, 26.11, 14.72, and 12.48 ng/L in global estuarine and coastal water, respectively (Fig. 6a). High concentrations of sulfonamides were frequently reported (Fig. 6a, b), some of which even exceeded the threshold of ecological risks (Tables S1 and S2) (Mijangos et al., 2018; Zhang et al., 2012). According to a survey from the estuarine environments of Basque Country, Spain, a median of 29.25 ng/L of CIP, 8.25 ng/L of SD, 18.75 ng/L of SMX, and 10.25 ng/L of TMP were determined in the estuarine water, as a result of the urban sewage discharge (Mijangos et al., 2018); the risk quotient (RQ) of SD showed a chronic-toxicity risk for aquatic organisms (Mijangos et al., 2018). Similar potential ecological risks caused by sulfonamides were also identified in Laizhou Bay (Zhang et al., 2012), Kroean coast (Kim et al., 2017), Mar Menor lagoon (Moreno-González et al., 2014), and Baltic Sea (Kötke et al., 2019). For instance, up to 6.60 of RQ for SMX was observed in the brackish water of German Bight, which was much greater than the risk threshold (RQ = 1) (Kötke et al., 2019).

Sulfonamide resistance genes, including *sul1*, *sul2*, and *sul3*, showed average abundances of 1.46×10^{-2}, 3.55×10^{-2}, and 6.20×10^{-4} copies/16S rRNA in estuarine and coastal environments across the globe, respectively (Fig. 6c). Previous studies have illustrated that sulfonamide resistance genes were co-enriched by antibiotics and heavy metals (Guo et al., 2018; Zhang et al., 2019). For instance, remarkable associations of ARGs with antibiotics and heavy metals (Pb, Cu, Cd, Cr and so forth) were observed in Feiyunjiang River Estuary, Oujing River Estuary, and Aojiang River Estuary (Lu et al., 2020). This phenomenon was also evidenced in Liaohe River Estuary (Lu et al., 2015), Laizhou Bay (Li et al., 2018b), and Yangtze River Estuary (Guo et al., 2018). However, positive connections between heavy metals and ARGs did not always exist (Zhang et al., 2019). In Port Philip Bay, Mn, Fe, Zn, and Cu all showed strong and negative associations with ARGs, and the mechanism underlying such a connection remains unclear (Zhang et al., 2019).

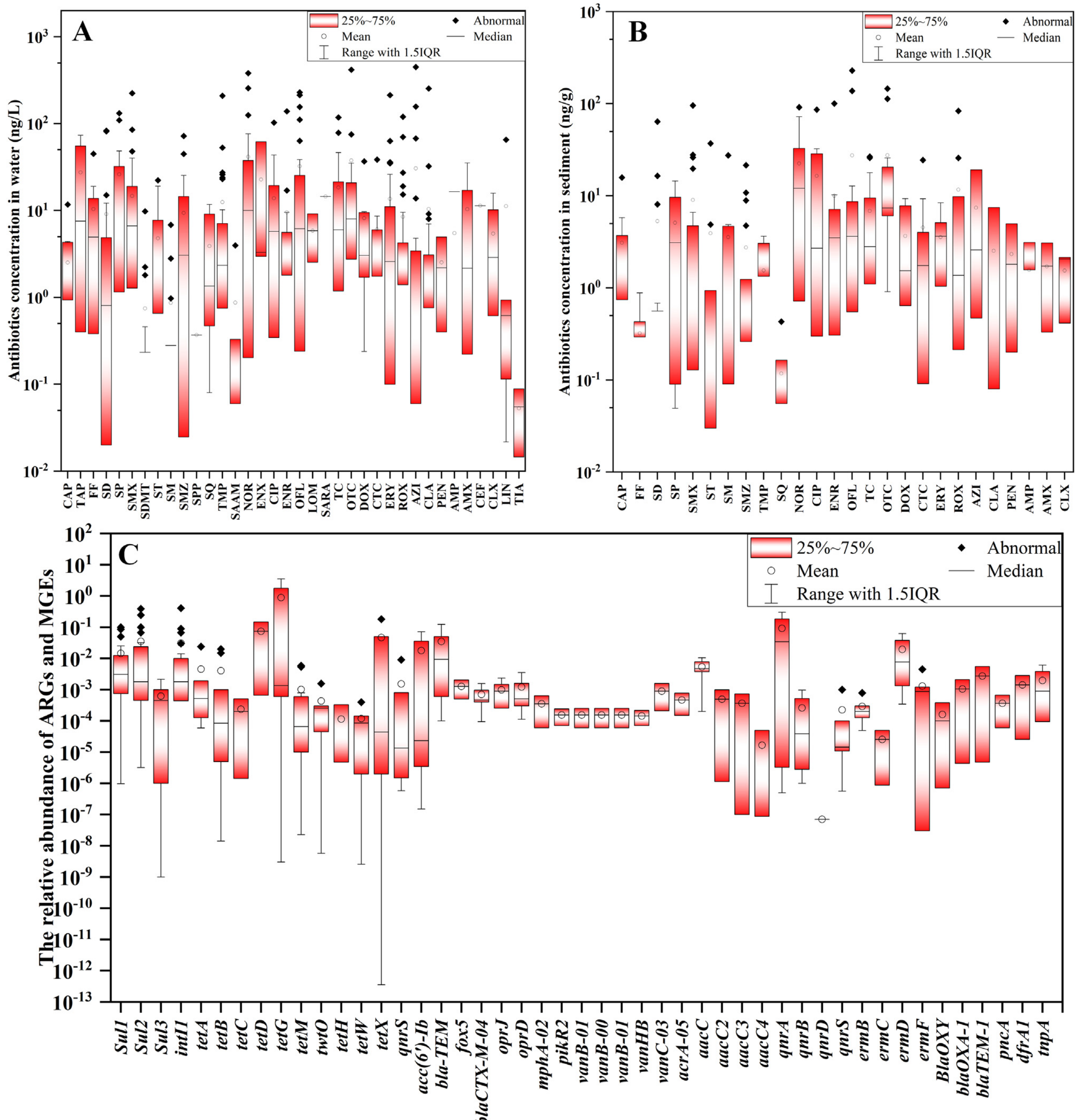

Fig. 6. The global abundances of antibiotics and ARGs. Concentrations of antibiotics in water (A) and sediment (B). Relative abundances (copies/16Sr RNA) of ARGs and MGEs (C).

Hence, the relationship between ARGs and heavy metals needs further studies.

4.5. Macrolides and macrolide resistance genes

ERY, ROX, AZI, and CLA were the most reported macrolides in estuarine and coastal water, showing the average concentration of 13.05, 5.37, 11.60, and 2.77 ng/L, respectively (Fig. 6a). The average concentration of ERY, ROX, AZI, and CLA in coastal sediment reached 3.56, 11.68, 7.42, and 2.52 ng/g, respectively (Fig. 6b). High ecological risk has been observed for some macrolides. For example, 0.40 to 1.66 ng/L of CLA would inhibit the growth of *Skeletonema marinoi* in the Germany Bight, resulting from coastal WWTP pollution (Kötke et al., 2019). Likewise, ERY, ROX, and CLA were revealed a high toxicity effect to *P. subcapitata* in LaiZhou Bay, where coastal water was contaminated by anthropogenic antibiotics from riverine runoff (Zhang et al., 2012). Moreover, some studies noted that the co-occurrence of multiple antibiotics would pose higher ecological risk, though individual antibiotics were not sufficient to pose threats to aquatic organisms (Du et al., 2017; Du et al., 2019; Zhang et al., 2018b).

Genes encoding resistance to macrolides showed relatively high abundance in global estuarine and coastal environment, with the mean abundances of 2.92×10^{-4} copies/16S rRNA for *ermB*, 2.54×10^{-5} copies/16S rRNA for *ermC*, 1.96×10^{-2} copies/16S rRNA for *ermD*, 1.31×10^{-3} copies/16S rRNA for *ermF*, and 3.02×10^{-2} copies/16S rRNA for *ermT*, respectively (Fig. 6c). Owing to the pollution from riverine runoff, 1.31×10^{-2} copies/16S rRNA of *ermD* and 4.49×10^{-2} copies/16S rRNA of *ermF* were determined in Aojiang River Estuary (Lu et al., 2020), which were comparable with Turku archipelago (Muziasari et al., 2016) and Fujian coast (Lu et al., 2019a). These regions were characterized by developed aquaculture and extensive antibiotic usage (Lu et al., 2019a; Muziasari et al., 2016), confirming that increased ARG prevalence was largely attributed to anthropogenic inputs. The average abundance of *ermT* was 6.04×10^{-2} copies/16S rRNA in Fujian coast. In this region, high level of ARGs were linked with elevated microbial diversity and richness, and ARGs were mostly harbored by *Owenweeksia*, *Planetomyces*, and *Marinobacterium* (Lu et al., 2019a).

5. Drivers of antibiotics and ARGs

5.1. Drivers of antibiotics

Environmental variables, including heavy metals, nutrients, and organic pollutants, among others, are important driving factors for antibiotics and ARGs (Fig. 3, Tables S1–S3). The close relationships between environmental variables and antibiotics in estuarine and coastal waters (Fig. S4A, Table S5) and sediment (Fig. S4B, Table S6) were observed. The co-occurrence patterns between environmental variables and antibiotics were explored by network analysis (Fig. 7), which revealed significant and strong correlations between them in both water (Fig. 7A) and sediment (Fig. 7B). For instance, aniline was found to be correlated with TAP, ROX, DOX, OFL, CTC, and NOR in water (Fig. 7A), and PAHs were correlated with OFL, FF, CTC, OTC, NOR, and CIP in the sediment (Fig. 7B). Four modules were identified in water, where total organic carbon (TOC), OTC, SQ, and CIP were the hub nodes of each module (Fig. S5A). Five modules were detected in the sediment, where PAHs, Mg, and CRD were the hub nodes of the module with the most nodes (Fig. S5B).

Such impacts of environmental variables on antibiotics have also been widely confirmed by previous studies. A study from the Zhuhai coastal environments indicated that sulfonamides and tetracyclines were significantly affected by NH_4^+ and TN in water during the wet season and TN strongly controlled the distribution of fluoroquinolones during both the wet and dry seasons (Li et al., 2018a). The correlations between antibiotics and heavy metals, including Hg and Cu, were confirmed in Hailing Bay, China (Chen et al., 2015b). According to a study by Li et al. (2016), temperature was positively correlated with SMX and CIP in the Gaoqiao mangrove wetland, while it was negatively correlated with TET, ENR, and OFL. PAHs and aniline were found to increase with antibiotics in three estuarine environments of Wenzhou (Lu et al., 2019a). Environmental variables affect the degradation rate or adsorption ratio of antibiotics, and further play a role in determining the concentrations of the antibiotics (Elmolla and Chaudhuri, 2010; Homem and Santos, 2011; Kafaei et al., 2018; Li et al., 2016; Li et al., 2018a; Zhang et al., 2013a). For instance, increased dissolved organic carbon (DOC) was associated with elevated SMX and ERY along the tidal flats of Yangtze River Estuary, suggesting DOC as a carrier of antibiotics (Zhao et al., 2015). Besides, a survey in Hailing Bay, China, found that high pH value might reduce the transmission of anionic TET from water to sediment.

Antibiotics used for veterinary and human consumption are mostly excreted into the environment because of their incomplete utilization (Ishikawa et al., 2018; Gao et al., 2018; Li et al., 2020a; Zhang et al., 2015a). As discussed in Section 3, anthropogenic activities have been considered the main source of antibiotics in the environment (Fig. 3, Tables S1 and S2), although natural bacteria also produce trace amounts of antibiotics (Crits-Christoph et al., 2018; Kumar et al., 2019). High concentrations of antibiotics have been ubiquitously detected in coastal aquaculture sites (Gao et al., 2018; Kim et al., 2017; Liu et al., 2017), effluent from WWTPs (Minh et al., 2009; Pärnänen et al., 2019; Pazda et al., 2019), and untreated sewage discharge (Divya and Hatha, 2019; Gupta et al., 2016; Qiao et al., 2018), confirming the significant contribution of anthropogenic activities to antibiotics in the environment. Furthermore, antibiotics and ARG inputs from rivers also support this viewpoint, as rivers are sinks of human-derived antibiotics from inland regions (Xu et al., 2013; Zhang et al., 2015a).

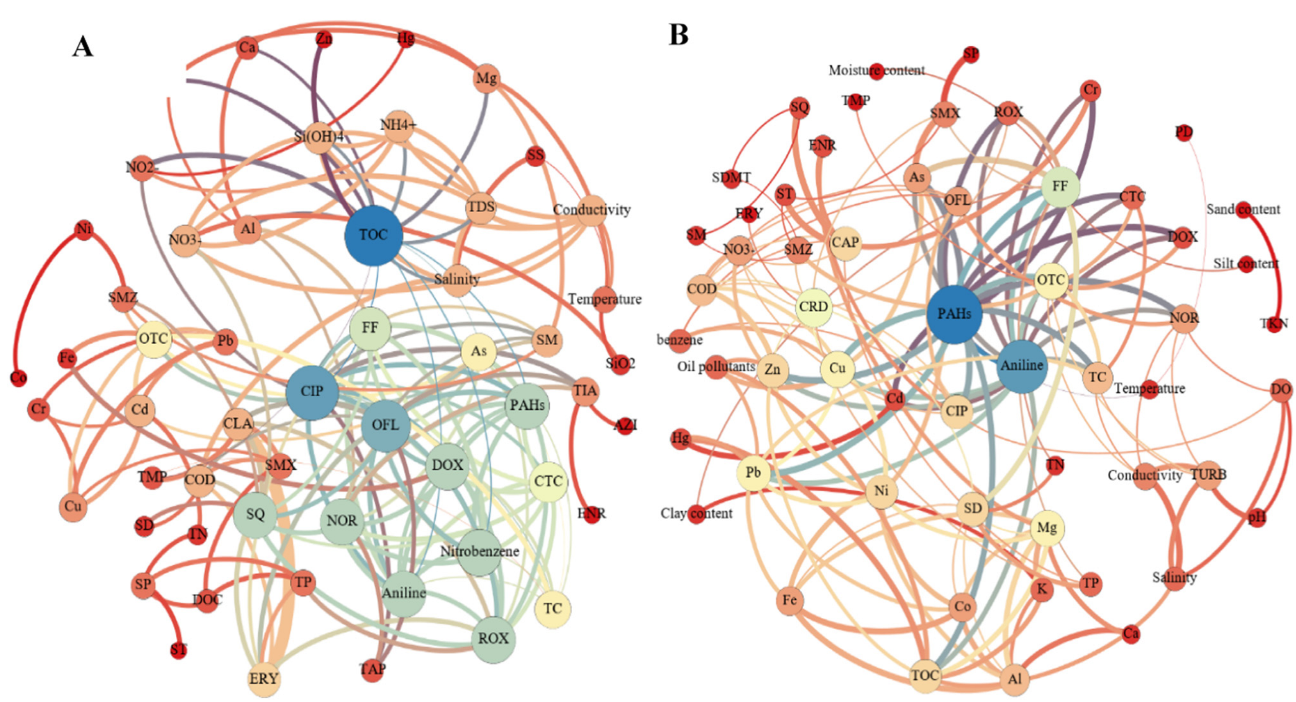

Fig. 7. Network analysis between ARGs and environmental variables. Network analysis showing co-occurrence patterns between environmental variables and antibiotics in estuarine and coastal water (A) and sediment (B). Each node corresponds to one of the environmental variables or antibiotics. The size of node is proportional to the connection number of nodes. The width of links increases with Spearman's correlation coefficient ($R > 0.7$, $p < 0.01$).

5.2. Drivers of ARGs

Most ARGs are obtained from the acquisition of ARGs that already exist in the microbial communities at background levels (D'Costa et al., 2011; Muziasari et al., 2016; Segawa et al., 2013). However, the presence of antibiotics allows bacteria to attain ARGs by gene mutation under antibiotic stress (Bakkeren et al., 2020). Antibiotics also pose selective pressure on microbes and enrich ARGs in estuarine and coastal environments (Bengtsson-Palme and Larsson, 2016; Duarte et al., 2019). Recent evidence from both controlled experimental settings and natural environments (Duarte et al., 2019; Xiong et al., 2015; Zhao et al., 2019b) revealed that antibiotics and ARGs are highly correlated. For instance, the study by Xiong et al. (2015) revealed that ARB with *tetM* and *tetX* were enriched through selective pressure posed by antibiotics. Another study (Duarte et al., 2019) confirmed that ARGs can be enriched under the selective pressure of antibiotics, even at low antibiotics levels. As a consequence of anthropogenic activities, antibiotics are prevalent in global estuarine and coastal environments and their concentrations vary from high (ppm) to low levels (ppt) (Desbiolles et al., 2018; Qiao et al., 2018); thus, antibiotic selective pressure may also vary widely in these environments.

Environmental factors are critical drivers influencing the abundance of ARGs (Fig. 3, Table S3). Heavy metals, such as Cu, Zn, and Cd, pose selective pressure on ARGs. Laboratory analyses have shown that heavy metals and antibiotics showed strong synergistic effects, and simultaneously enriched ARGs and heavy metal resistance genes (Chen et al., 2019; Ding et al., 2019; Lin et al., 2019). This phenomenon was also confirmed in estuarine and coastal environments, where significant associations between heavy metals and ARGs were found (Guo et al., 2018; Li et al., 2018a; Lu et al., 2015). Nutrients, including various chemical forms of C, N, P, and K, are another important driving factor for ARGs, as they contribute to the growth of bacteria carrying ARGs and facilitate the sorption of sediment to ARGs (Lu et al., 2019a; Zhao et al., 2019a). Organic pollutants, such as PAHs and microplastics, are also responsible for the abundance of ARGs due to their co-selection and enrichment to the latter (Bhattacharyya et al., 2019; Dong et al., 2021; Lu et al., 2019a; Wang et al., 2017; Wang et al., 2020; Yang et al., 2019). For instance, aquaculture water in Fujian Province, China, was detected to harbor 58–72 items/m^3 in microplastics, where ARGs in microplastics were higher than those in coastal water by four orders of magnitude (Lu et al., 2019a). Most previous studies (Dong et al., 2021; Lu et al., 2019a; Wang et al., 2020; Yang et al., 2019; Zhang et al., 2020b) have revealed that the strong adsorption of microplastics to microbes was responsible for the enrichment of ARGs in estuarine and coastal environments, partly resulting from the existence of biofilms that colonized by microorganisms carrying ARGs. A study from Port Philip Bay, Australia, revealed that beach soil is a reservoir of ARGs in coastal environments and that salinity functions as a dominant factor controlling the distribution of ARGs (Zhang et al., 2019). Moreover, the impact of temperature and pH on ARGs cannot be ignored. Our analysis in Section 4.1 revealed the complicated relationships between temperature and ARGs on a global scale; however, these results could not be necessarily observed on a smaller scale (Li et al., 2018a; Lu et al., 2015). Similar to temperature, pH exerts complex effects on ARGs (Su et al., 2020b; Zhao et al., 2019a); pH was negatively related to *arnA* but positively associated with *mdtB* (Zhao et al., 2019a), confirming that different bacteria have different optimal pH conditions (Ahmed et al., 2020; Li et al., 2020b).

Apart from antibiotic residues and environmental variables, the abundance of ARGs was partly explained by the microbial community, as microbes can be the hosts of ARGs (Fig. 3, Table S3). Research conducted by Zhao et al. (2019a) revealed that 50 classes of bacteria were significantly related to antibiotic resistance variables (ARVs, including resistance types, resistance mechanisms, abundances, and diversities of ARGs) in mangrove sediment of the South China Sea; 11.5% of ARG variation could be explained by the bacterial community. *Cyanobacteria*, *Proteobacteria*, *Bacteroidetes*, *Actinobacteria*, *Firmicutes*, *Planctomycetes*, *Verrucomicrobia*, and *Chloroflexi* were the dominant phyla in global estuarine and coastal environments (Lu et al., 2019a; Su et al., 2017; Zhang et al., 2019; Zhao et al., 2019a; Zhu et al., 2017), some of which were identified as potential hosts of ARGs. The significant correlations between ARGs and bacterial communities confirmed these relationships. For instance, Zhu et al. (2017) reported that *tnpA*, *tetA*, *tetO*, *tetM*, *aadA2*, and *aphA3* were strongly correlated with *Proteobacteria*, *Firmicutes*, and *Bacteroidetes* and that such bacteria were the possible hosts of these ARGs. Many studies (Lu et al., 2019b; Su et al., 2017; Xu et al., 2019) have identified the potential hosts of ARGs at the phylum level using network analysis between ARGs and microbes. Further studies could use machine learning, proximity-ligation methods (Stalder et al., 2019), and metagenomics to identify ARB at the genus and species levels.

HGT also contributes to the dissemination of ARGs in estuarine and coastal environments (Fig. 3, Table S3), resulting from the propagation mechanisms of transformation, transduction, and conjugation (Brigulla and Wackernagel, 2010; Husnik and Mccutcheon, 2017; Wellington et al., 2013). Transformation, or so-called natural genetic transformation, indicates the active uptake and genomic integration of microbes to extracellular DNA. Transduction refers to bacteriophages transferring nonviral DNA from donor microbes to recipient microbes. Conjugation denotes DNA translocation from the donor microbe to the recipient microbe when two microbes are in contact, and is driven by MGEs. Integrons, insertion sequences, transposons, and plasmids are the major MGEs, of which integrons, including *intI1*, *intI2*, *intI3*, and *intI4*, are the most widely reported in estuarine and coastal environments. Significant associations between ARGs and integrons have been discovered in the estuarine and coastal environments of Australia (Zhang et al., 2019), China (Chen et al., 2019; Chen et al., 2020a; Leng et al., 2020; Niu et al., 2016; Zhao et al., 2019a; Zhu et al., 2017), Finland (Muziasari et al., 2016), and even Antarctic (Na et al., 2019). Sewage, from a variety of sources, that accumulates in WWTPs functions as a hotspot of ARGs and MGEs, that in turn, facilitates HGT (Rizzo et al., 2013; Zhang et al., 2020b). Conventional wastewater treatment techniques do not effectively eliminate ARGs and MGEs, resulting in their high concentrations in the effluents of coastal WWTPs; hence, coastal environments coming into contact with such effluents may become heavily polluted by ARGs (Fresia et al., 2019; Germond and Kim, 2015).

6. Environmental implications of antibiotics and ARGs

6.1. Microbial communities

The effects of antibiotics and ARGs on microbial communities have engendered great interest (Allen et al., 2010; Hagenbuch and Pinckney, 2012; Piotrowska-Długosz, 2017; Turker et al., 2018). The response of microbes to antibiotics was typically dose-dependent (Andersson and Hughes, 2014). At high concentrations, antibiotics induce antibacterial action on susceptive bacteria (Grenni et al., 2018). The existence and persistence of antibiotics have been demonstrated to reduce microbial diversity and to alter the structure of microbial communities (Ding and He, 2010; Harrabi et al., 2019). Under the pressure of antibiotics, ARBs tend to acquire more nutrients or space to proliferate and thus leading to an elevated relative abundance of ARBs, compared with susceptive bacteria (Andersson and Hughes, 2014; Grenni et al., 2018). Antibiotics below minimal inhibitory concentration are capable of enriching for pre-exposed resistant bacteria and selecting for de novo resistance (Grenni et al., 2018). Besides, sublethal dose of antibiotics has long term effects on bacterial physiology, including increasing genetic and phenotypic variability (Andersson and Hughes, 2014). As an example, aminoglycoside streptomycin was found to result in translational errors and phenotypic variability (decreased growth rate) (Davies et al., 1964). Interestingly, low dose of antibiotics would serve as signaling molecules between bacteria, further resulting in multiple functional consequences (Aminov, 2009), such as biofilm formation, quorum sensing, bacterial virulence, as well as gene expression (Davies, 2013; Dietrich et al., 2008; Romero et al., 2011).

The impact of antibiotics and ARGs on microbial communities has been widely evidenced in global estuarine and coastal environments (Tables S1–S3). Harrabi et al. (2019) reported that the richness and diversity of microbial community decrease after 10-day incubation with 1 mg/L ENR and OXY in sediment of Douro River Estuary. During the incubation process, the dominant phyla altered from *Proteobacteria* and *Bacteroidetes* to *Proteobacteria*, while the predominant genera transferred from *Xanthobacter*, *Sphingobium,* and *Leucobacter* to *Fluviicola*, *Sphingobium*, *Fusibacter*, *Comamonas*, and *Stenotrophomonas* (Harrabi et al., 2019). Another study conducted by Näslund et al. (2008) indicated that the microbial structure of experimental group (exposed to 200–2000 μg/L of CIP) was significantly distinct from that of the control group, based on pairwise analyses of similarities using the Bray-Curtis distance measure. In the Yangtze River Estuary, an addition of 0.3–56.8 ng/L of SMX remarkably reduced the abundance of ammonia oxidizing bacteria, thus resulted in increased N_2O production during 20-day continuous-flow experiments (Chen et al., 2020b). Likewise, during 8-hour incubation experiments, SMT addition was observed to reduce the abundance of denitrifiers and to enrich *sul1* in sediment of the Yangtze River Estuary (Hou et al., 2015). Apart from estuarine and coastal environments, similar impacts of antibiotics on microbial communities have also been evinced by those studies conducted in sewage sludge, soil, and manure (Bai et al., 2019; Ding and He, 2010; Gutiérrez et al., 2010; Liu et al., 2012; Zhang et al., 2013b).

6.2. Biogeochemical cycles

Antibiotics and ARGs also disturb the biogeochemical cycling processes (Roose-Amsaleg and Laverman, 2016), including nitrogen cycle (DeVries and Zhang, 2016; Hou et al., 2015; Toth et al., 2011; Yin et al., 2016), carbon cycle (Conkle and White, 2012; Liu et al., 2014), sulfur cycle (Ingvorsen et al., 2003; Liu et al., 2014), phosphorus cycle (Lu et al., 2018a), pyrene degradation (Näslund et al., 2008), and the oxidation and reduction of heavy metals (Toth et al., 2011; Yamamura et al., 2014). Most play a role by changing the bacterial communities related to biogeochemical cycles (Fig. 3). For instance, 50 ng/L SMZ decreased denitrification rates by 20–30% in the Yangtze Estuary, resulting from the 39–53% reduction of denitrifying functional genes (Hou et al., 2015). Likewise, Yamamura et al. (2014) explored the impact of antibiotics, including CAP, AMP, LIN, TET, and ERY, on microbial redox transformations of arsenic in sediment. Their results indicated that CAP reduced the diversity of arsenite-oxidizing bacteria, thereby reducing arsenate (90%) and increasing arsenite (400%) (Yamamura et al., 2014). Additionally, >200 μg/L of CIP in marine sediment was found to significantly inhibit the mineralization of pyrene and reduce 90% CO_2 emission because of the inhibition of microbial growth (Näslund et al., 2008).

Although some impacts of antibiotics and ARGs on biogeochemical cycles were found in soil and wastewater, these were also likely to occur in estuarine and coastal environments. In soil, the addition of poultry manure containing SMZ altered bacterial composition and further raised nitrate emissions by about 300% during 56 days of incubation (Awad et al., 2016). Similarly, Toth et al. (2011) revealed that manure with 10–200 ng/g SDMT and monensin increased iron reduction by 375% and 240%, respectively, resulting from the inhibitory effect of antibiotics on microbial activities. In wetland soil, the CO_2 release rate was inhibited owing to the change in microbial respiration rate in the presence of 500–1000 ppb of SMZ (Conkle and White, 2012). In wastewater, Lu et al. (2018b) explored the relationship between TC occurrence and PH_3 release, showing that lower pH increased dehydrogenase activity and promoted the production of PH_3 upon exposure to TC.

6.3. Potential health threats

Antibiotic transmission from the environment to marine organisms and humans is also a serious concern (Fig. 3, Tables S1–S2). Many studies have revealed the potential bioaccumulation and biomagnification of antibiotics in marine organisms (Li et al., 2012b; Liu et al., 2018b; Na et al., 2013; Puckowski et al., 2016; Zhang et al., 2020c), highlighting the health impacts of long-term antibiotic exposure. In three estuaries of Seattle, 17 ng/g CIP was detected in the body of *sculpin* even though this compound was only 7.3 ng/L in the estuarine water (Meador et al., 2016). Besides, up to 0.71–1715.10 ng/g fluoroquinolones was detected in mollusks from the Bohai Sea of China, where mollusks are one of the most popular seafood, suggesting that the consumption of mollusks would pose potential health risk to local residents (Li et al., 2012b). In fish from coral reef of the South China Sea, the highest log-transformed bioaccumulation factor (BAF) of ENX exceeded 3.7 and its trophic magnification factors (TMF) reached 2.7, indicating the existence of bioaccumulation effect (BAF > 3.7) and magnification effect (TMF > 1) (Zhang et al., 2020c). Similar results were observed in a subtropical food web of the Beibu Gulf (1.58 for ENX) (Wu et al., 2020) and Laizhou Bay (2.19 for SMX and 2.40 for TMP) (Liu et al., 2017). These values in estuarine and coastal environments were greater than those previously observed in lakes and rivers, such as ROX (0.50) in Qinhuai River (Yang et al., 2020), SMX (0.50) and ROX (1.11) in Taihu Lake (Xie et al., 2015; Zhou et al., 2020), NOR (1.24–1.25) and ENR (1.08–1.10) in Baiyangdian Lake (Zhang et al., 2020d).

Long-term exposure to antibiotics shapes the gut bacteria, immune function, growth, reproduction, and digestion in marine organisms (Gaw et al., 2014; Qiu et al., 2020; Sun et al., 2020b; Zhao et al., 2019b). For example, ROX was found to increase the specific growth rate of sea cucumbers by 0.4% during a 45-day experiment, where mortality increased by 1.67%. The increasing mortality was considered to be responsible for higher levels of antibiotic resistance (Zhao et al., 2019b). Furthermore, antibiotics were transferred to the human body through food intake (Ben et al., 2019; Li et al., 2017; Wang et al., 2015), affecting the body weight and gestational age of newborns (Zhao et al., 2019c), gut bacterial community (Raymond et al., 2016), and antibiotic resistance (Tang et al., 2017). For example, Zhao et al. (2019c) reported that the detection rate of CTC, PEN, and CAP reached 43.9%, 16.5, and 10.8% in newborns, respectively, and the concentration of PEN was positively associated with newborn body weight. Considering the prevalence of antibiotics in seafood (He et al., 2019; Klosterhaus et al., 2013; Meador et al., 2016; Mijangos et al., 2018), the transmission of antibiotics from estuarine and coastal environments to the human body can be considerable.

Apart from antibiotics, ARGs could transfer from the environment to marine organisms and the human body (Fig. 3). Aquaculture activities are hot spots of ARG pollution in estuarine and coastal environments (Gao et al., 2018; Kim et al., 2017; Liu et al., 2017; Wu et al., 2019), where the prevalence of ARGs rendered the antibiotics useless, and the aquaculture organisms became more vulnerable to diseases (Singh et al., 2017; Zhao et al., 2019b). This led to huge economic losses in aquaculture (Founou et al., 2016; Mohamad et al., 2019; Reverter et al., 2020). In human bodies, ARGs are transferred through direct (such as swimming) or indirect contact (such as seafood intake) with the environment (Fig. 3). Leonard et al. (2015) indicated that 0.12% of the *E. coli* in the coastal bathing water of England and Wales was resistant to cephalosporins, implying that the recreational exposure of ARB in seawater is underestimated. In addition, recent studies (Jang et al., 2018; Jiang et al., 2019; Kumaran et al., 2010) have indicated that ARB and ARGs are highly prevalent in seafood, such as marine fish, shrimp, and mussel. For example, mariculture farms in the Bohai Sea and Yellow Sea showed that 44.4% of *V. parahaemolyticus* isolates were resistant to multiple antibiotics in shrimp, shellfish, sea cucumber, and half-smooth tongue sole (Jiang et al., 2019). Infectious dose of different ARBs showed significant variations, for example, *Vibrio cholerae* requiring 10^3–10^8

cells and *Streptococcus pneumonia* demanding 10^5–10^6 cells; however, only 10 *E. coli* particles are enough to infect an individual (Schmid-Hempel and Frank, 2007). Of particular concern is that the infectious risk of pathogens would increase when people were exposed with impaired immune system (Leonard et al., 2015), which suggested high infectious risk of ARB at a very low-dose exposure (Manaia, 2017). Therefore, human health risks through the intake of contaminated seafood or owing to the contact with polluted aquatic environments was a great concern (Amarasiri et al., 2020; Huijbers et al., 2015).

7. Research challenges and future prospects

Despite the broad recognition of anthropogenic activities as the main pollution sources of antibiotics and ARGs in estuarine and coastal environments (Ali et al., 2017; Alygizakis et al., 2016; Kim et al., 2017; Lu et al., 2015; Xu et al., 2013), quantifying the specific proportion of each anthropogenic source is still a challenge. This is largely ascribed to lack of the consumption statistics of antibiotics, expensive metagenomic techniques, as well as short of robust mathematic methods for quantitative source-apportionment. Recent advances in machine learning techniques combined with metagenomics are expected to provide a reliable solution (Knights et al., 2011; Shenhav et al., 2019; Li et al., 2018c). SourceTracker based on Bayesian theory and Gibbs sampling has been applied to differentiate microbial sources (Knights et al., 2011). Recently, FEAST, based on the expectation-maximization algorithm, has been developed to perform such work at a faster rate and a higher accuracy (Shenhav et al., 2019). The two methods (Knights et al., 2011; Shenhav et al., 2019) require complete ARG profiles from both source samples and sink samples, which is difficult for quantitative polymerase chain reaction (qPCR) with limited detection capacity but not for metagenomics. While SourceTacker and FEAST with metagenomics have been sporadically applied to quantify ARG sources in Pearl River Estuary (Li et al., 2018c) as well as Lake Baiyang (Chen et al., 2020c), more applications in the future are expected to better understand the sources of ARGs.

Limited studies from low- and middle-income countries hamper the acquisition of comprehensive understandings on antibiotics and ARGs in coastal environments. The prevalence of antibiotic resistance was inversely associated with antibiotic consumption, infrastructure, GDP per capita, education, as well as public health-care spending (Collignon et al., 2018). Low- and middle-income countries (African and Latin American countries in particular) are characterized by poor infrastructure, inferior education level, lower GDP per capita, and limited public healthcare spending (WHO, 2014). Increasing antibiotic consumption for human and veterinary purpose have been reported in these countries (Högberg et al., 2014; Klein et al., 2018; Van Boeckel et al., 2014; Versporten et al., 2014). Environmental problems and human health risks induced by antibiotic and ARG pollution are likely to be more prevalent in these countries. Therefore, antibiotics and ARGs in estuarine and coastal environments of the low- and middle-income countries should be prioritized in future studies.

Due to the lack of understandings and data on environmental and health risks, evaluating and modelling long term impacts of antibiotics and ARGs on ecosystems and humans remain challenging. For instance, significant associations between temperature and antibiotic resistance have been evinced by many studies (MacFadden et al., 2018; Dunivin and Shade, 2018; Lin et al., 2017); however, the mechanism underlying such a connection is largely unclear. This knowledge gap has limited our ability to evaluate the outbreak risk of antibiotic resistance in coastal ecosystem under different global change scenarios. Additionally, the responses of a single biogeochemical process to antibiotics have been frequently discussed (Hou et al., 2015; Liu et al., 2014; Lu et al., 2018b; Roose-Amsaleg and Laverman, 2016). Nevertheless, the joint responses of various biogeochemical cycles to antibiotics are not well understood, which make it difficult to model the emission dynamics of greenhouse gases in estuarine and coastal environments under the interfere of antibiotic residues. Moreover, despite the discovery of convincing evidence that ARGs transfer from livestock farms to the human body (Sun et al., 2020b), our understanding regarding ARG transmission from estuarine and coastal environments to humans is still lacking. The significance to evaluate the health risks of ARGs in mariculture has been controversial.

The wide occurrence of antibiotics and ARGs in estuarine and coastal environments is partly ascribed to conventional WWTPs failing to effectively eliminate antibiotics and ARGs in wastewater (Bao et al., 2020; Guo et al., 2017; Mao et al., 2015). As a consequence, mitigation measures for the existing pollution are urgently required. Some novel wastewater treatment techniques, such as anaerobic treatment (Yi et al., 2017), ionizing radiation (Chu et al., 2019; Chu et al., 2020), and photoelectrocatalytic treatment (Jiang et al., 2017), should be promoted. For example, ionizing radiation (Chu et al., 2020) has been shown to effectively remove 74% and 86% of antibiotics and ARGs, respectively. More importantly, strict policies to reduce the abuse of antibiotics are necessary in clinical settings, veterinary environments, and aquaculture. A systematic surveillance network of antibiotics and ARGs in urban sewage, livestock farms, aquaculture, WWTPs, and seafood should be developed. Moreover, public education should be conducted to raise awareness about the proper use of antibiotics to alleviate antibiotic abuse and ARG dissemination in the environment.

8. Conclusions

This review showed that the prevalence of antibiotics and ARGs in estuarine and coastal environments is largely attributed to anthropogenic activities, including contaminated riverine runoff, WWTPs, sewage discharge, as well as aquaculture. Antibiotic concentrations in low- and middle-income countries were significantly higher than those in high-income countries, and ARGs exhibited pronounced latitude gradients. The distribution of ARGs follow distance decay law at a global and continental scale. The distributions of antibiotics were regulated by environmental variables and anthropogenic activities, while ARGs were driven by antibiotic residues, environmental variables, microbial community, as well as MGEs. Antibiotics and ARGs in estuarine and coastal environments altered microbial communities, thus indirectly disturbing biogeochemical cycles. The prevalence of antibiotics and ARGs posed potential threats not only to marine organisms but also to humans.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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