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Antibiotics in global rivers

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Abstract: Antibiotics have received extensive attention due to their sophisticated effects on human health and ecosystems. However, there is an extreme scarcity of information on composition, content, geographic distribution, and risk of riverine antibiotics at a large spatial scale. Based on a systematic review of over 600 pieces of literature (1999–2021), we established a global dataset containing more than 90,000 records covering 169 antibiotics and their metabolites in surface water and sediment across 76 countries. The occurrence of prioritized antibiotics largely depended on socioeconomic developmental levels, and the current "hotspots" of polluted rivers were found mostly in less developed countries or emerging economies (e.g., some in Africa, South America, and Asia). By developing the screening protocol for risk-based prioritization of antibiotics, we advanced a rank list of antibiotics for guiding formulation of region-specific strategies, which highlighted the importance of whole life cycle management of antibiotics in health maintenance of the world's rivers.

Keywords: antibiotics, river, water, sediment, risk, prioritization

Introduction

Antibiotics are of primary importance to human health [1]. So far, more than 600 different antibiotics have been used in the field of prevention and therapy of human and animal illnesses worldwide [2]. The global antibiotic consumption was estimated about 42 billion defined daily doses (DDDs) in 2015, and would be further increased by 200% in 2030 [3]. A major fraction of antibiotics consumed by human and animals are excreted in the parent form or active metabolites via urine and faeces [4], and then enter the surface water through the effluents of wastewater treatment plants (WWTPs) [5–7], aquaculture and animal husbandry wastewater [8,9], and agricultural runoff [10]. In the past two decades, the contamination of cocktails of

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antibiotics in surface water and sediment has been continuously reported, including occurrence [11–13], spatiotemporal distribution [14–16], risk assessment [16–18], and effective management [14,19,20] of antibiotics in rivers worldwide [21]. Besides accelerating the propagation of antibiotic resistance genes (ARGs) [22–28], antibiotics also pose potential ecological risks to aquatic organisms [20,29,30]. Dangerous levels of antibiotics have been alarmed in many rivers [30–32], e.g., the environmental concentration of sulfamethoxazole (SMX) was found to have exceeded its predicted no-effect concentration to aquatic organisms at 140 of 1052 study sites (13%) in global rivers, and the concentration of trimethoprim (TMP) over the safe target for antimicrobial resistance appeared in a variety of rivers from Africa and South America [33]. With rocketing consumptions of antibiotics [3,34], their occurrence and risk in surface water will receive increasing attention in the future.

As a global challenge across different regions, antibiotic prevelance in aquatic environments is closely related to human activities and regional socioeconomic development [35,36], suggesting the necessity of integrated study on developmental trends, drivers, and controlling strategies of antibiotic contamination. However, the comprehensive understanding on antibiotics associated with natural, social, and economic variables in various river basins relies on mining plentiful surveillance data from numerous sources and integrating the vast dataset for accurate identification of the priority antibiotics [11,37–39]. With an overview of the studies on riverine antibiotics, we established a global dataset encompassing more than 90,000 records of 169 antibiotics and their metabolites in water and sediment. Consequently, we revealed the diversity of composition and content of antibiotics, identified the hotspots of antibiotic pollution, and provided a risk-based framework for prioritization of antibiotics at regional and global levels. This study indicated the necessity of developing basin- and region-specific strategies for antibiotic pollution control in terms of varying developmental stages, and highlighted the importance of the whole life cycle management of antibiotics through sectoral, regional, and international collaborations.

Occurrence and distribution of antibiotics

Dataset establishment

By review of more than 600 papers published from 1999 to 2021, we established a dataset based on 72,243 records of antibiotics in water and 20,439 in sediment of the rivers distributed in 7 continents (Table S1 and Figure S1, Supporting Information). Totally, 8860 and 2569 sampling sites covering 76 countries as well as Polar regions were surveyed (Figure 1A and 1B). Early evidence of occurrence of antibiotics in surface water can be traced back to 1999 [40]. Later on, more efforts have been made to develop analytical methods [41–45] for accurate detection of antibiotic occurrence [46,47], and further expanded to source apportionment [48] and risk assessment in recent years [49–52]. More recently, antibiotics are investigated with more attention to their linkages with ARGs [53–59].

In our global dataset, a total of 169 types of antibiotics and their metabolites (160 in surface water and 111 in sediment) were identified (Figure 1C–1F). These antibiotics were further categorized as six classes (Table S2) such as sulfonamides (SAs, 36), tetracyclines (TCs, 18), quinolones (QNs, 28), β-lactams (β-Ls, 29), macrolides (MLs, 23), and others (35). Among them, the dissolved antibiotics were from 63 countries (Figure 1C) and sedimentary antibiotics from 30 countries (Figure 1D). The dataset contains a large number of

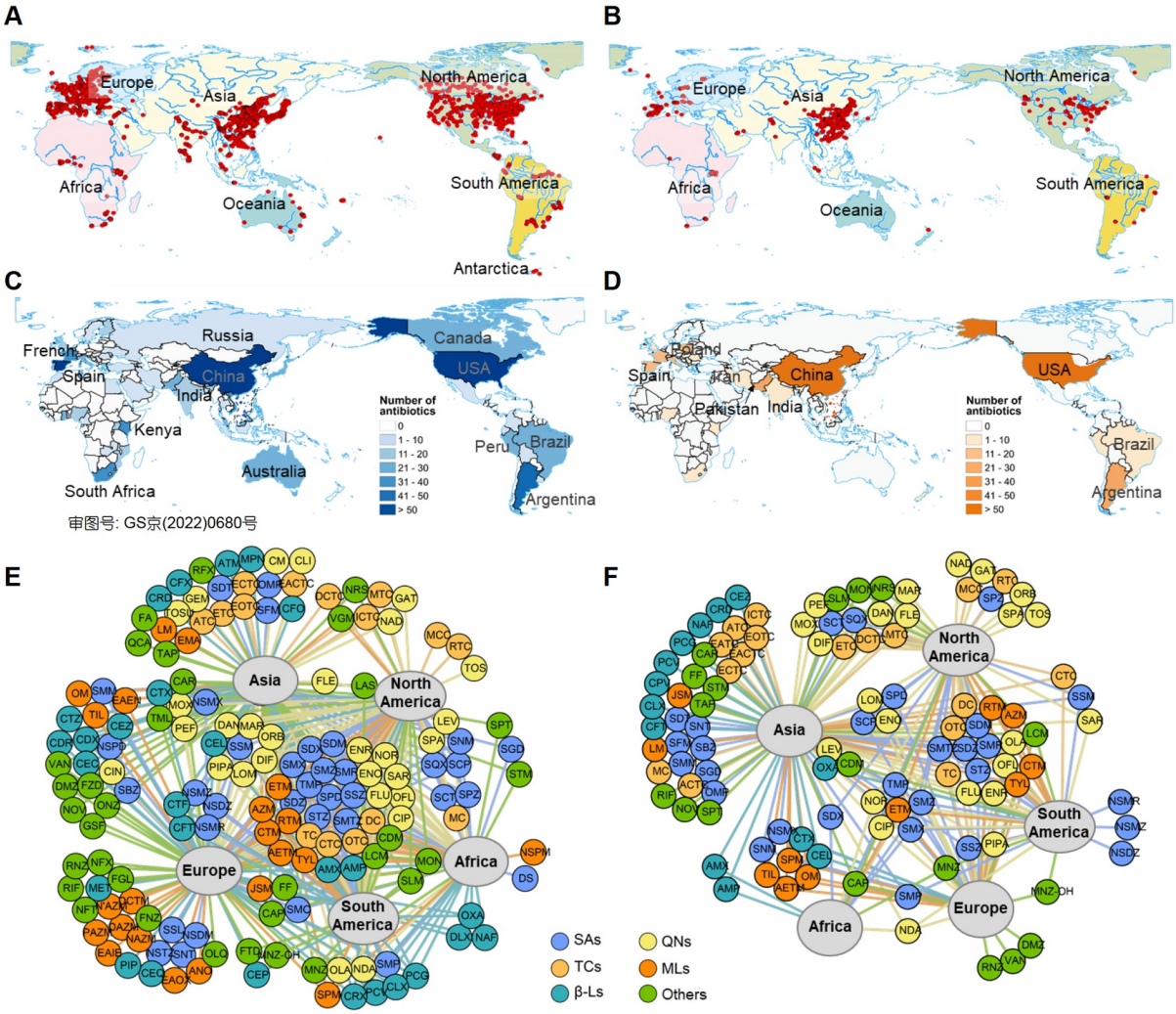

Figure 1 Occurrence of the examined antibiotics in world's rivers. Geographical distribution of sampling sites (red dots) in river water (A) and sediment (B). Number of the reported antibiotics in river water (C) and sediment (D) from different countries. Venn plot of the antibiotic types in river water (E) and sediment (F) from different continents (The abbreviations for the full names of antibiotics are given in Table S2).

examined antibiotics from China (126 in water and 93 in sediment) [4], USA (63 and 54), Spain (84 and 19), and other countries in Asia, Europe, Africa, North America, and South America, but much less from Oceania and Antarctica due to data access difficulties. Of the 32 dissolved (Figure 1E) and six sedimentary (Figure 1F) antibiotics shared by the five continents, sulfamethazine (SMZ), SMX, TMP, ciprofloxacin (CIP), norfloxacin (NOR), and erythromycin (ETM) were the most frequently detected due to their extensive consumption [60].

Besides the types of antibiotics, the number of records for each of the six classes was also summarized in the five continents (Figure S1). As the first clinically successful broad-spectrum antibiotics [4,8], SAs were no doubt the class with the largest number of records in the four continents except South America, notably represented by SMX (data item 269–2597) and TMP (271–1942) in water. Due to their low cost and effectiveness against a broad range of infections, SMX and TMP were often used in combination and thereby

simultaneously occurred in natural waters [61].

Distribution of antibiotic concentration from the continental perspective

Due to the great difference in antibiotic types in varying rivers, only 32 shared antibiotics in water were compared (Figure 2 and Table S3), which belong to SAs, TCs, QNs, MLs, β-Ls, and lincosamides (LMs). The median concentrations of the 32 representative antibiotics ranged from ND to 286 ng/L in water from the five continents, and 90.0% of them were below 10.0 ng/L (Figure 2A). Among them, SMX, TMP, anhydroerythromycin (AETM), and amoxicillin (AMX) demonstrated relatively high concentrations, with median concentrations of 3.20–122, 1.51–78.0, 0.16–86.0, and ND–286 ng/L, respectively. Compared with

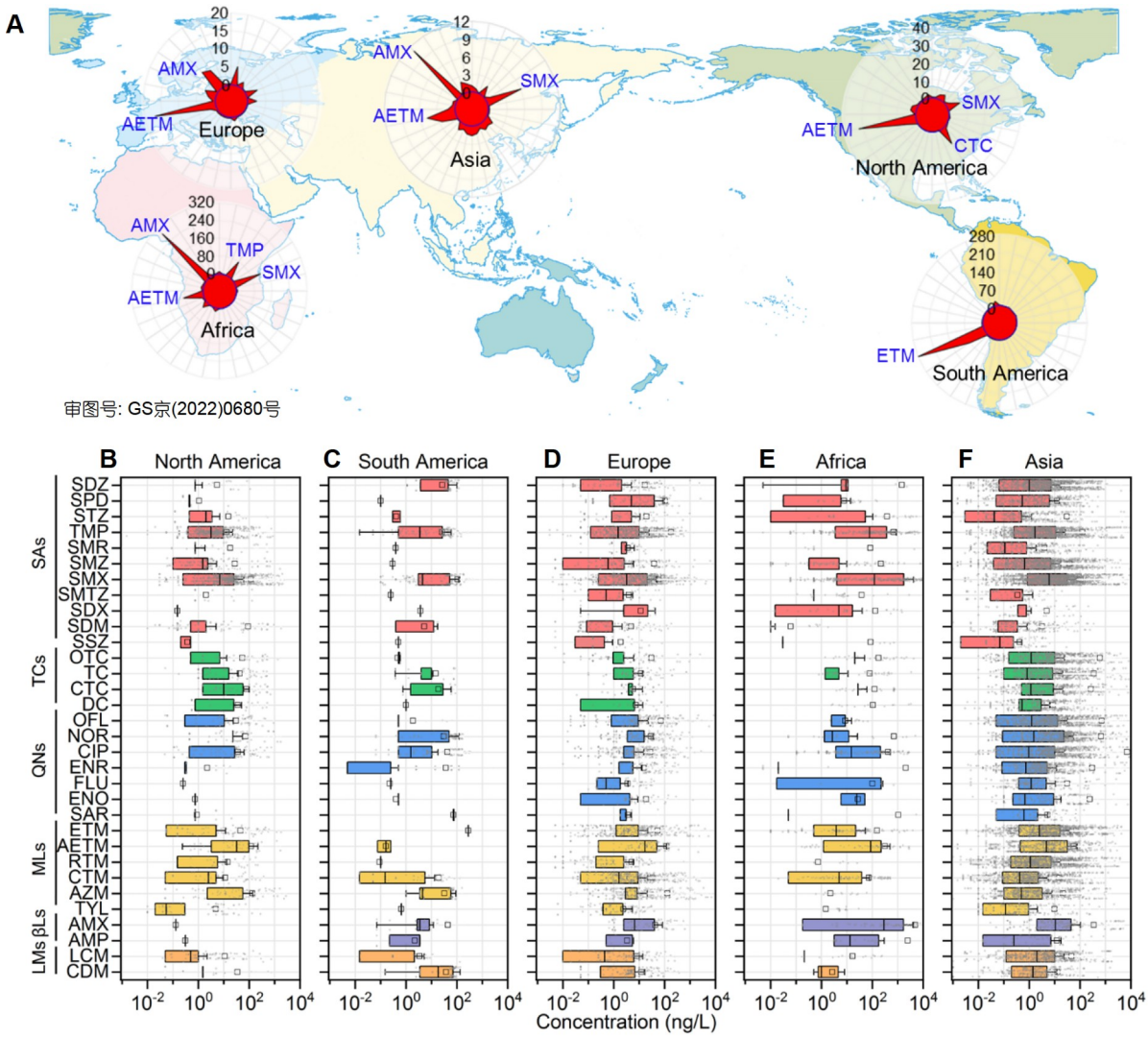

Figure 2 Concentrations of antibiotics in river waters of five continents. Median concentrations of 32 representative antibiotics (ng/L) in river waters of five continents (A). Boxplots of concentrations of 32 representative antibiotics in river waters from North America (B), South America (C), Europe (D), Africa (E), and Asia (F).

the other four continents, Africa more frequently displayed greater antibiotic concentrations (>100 ng/L). The median concentrations of SMX, TMP, AMX, and AETM in the water of Africa were 286, 122, 78.0, and 86.0 ng/L, respectively (Figure 2A and 2E), which were significantly higher than those in other continents (P<0.05, Figure S2A–S2D). The highest concentrations of SMX and TMP were up to 3320 [62] and 38.9 μg/L [63], respectivley, in rivers of Africa. The higher concentrations of antibiotics in Africa were interpretable because the rivers there suffered from the discharge of WWTP effluents with poorer treatment and management [62–65]. ETM and CTM were the most investigated MLs in water, with median concentrations of 1.25–280 and ND–5.00 ng/L, respectively (Figure S2E and S2F). CIP and oxytetracycline (OTC) were the most widely reported QNs and TCs in water, respectively, with median concentrations of ND–15.0 and ND–1.19 ng/L (Figure S2G and S2H).

A total of 11–91 antibiotics were detected in sediment from the five continents, with median concentrations ranging from ND to 1290 ng/g (Table S4). Six shared antibiotics were examined in sediment from the five continents (Figure 1F), but three of them (TMP, CIP, and ETM) were concurrently detected, with median concentrations of ND–0.72, ND–47.4, and ND–0.25 ng/g, respectively (Figure S3). The concentrations of TMP and CIP in Africa were significantly higher than those in sediment from other continents (P<0.05, Figure S3A and S3B), while the concentrations of ETM in Asia were higher than those in Europe and North America (P<0.05, Figure S3C). Since only limited antibiotics were detected in sediment from Africa (11) and South America (14), the concentrations of antibiotics in sediment from the other three continents were further analyzed. Twenty-three antibiotics were commonly detected in sediment from Asia, Europe, and North America, with median concentrations of ND–13.6, ND–8.96, and ND–1.70 ng/g, respectively (Figure S4A–S4D). In comparison, OTC, tetracycline (TC), ofloxacin (OFL), NOR, CIP, and flumequine (FLU) exhibited higher concentrations in sediment (Figure S4D), because TCs and QNs have high affinity to sediment resulting from their complexation with sediment organic matters and heavy metals [11,66]. SAs, MLs, and LMs displayed the median concentrations lower than 1.0 ng/g from these three continents except RTM (3.61 ng/g in Asia) (Figure S4D).

Distribution of antibiotic concentration from national perspective

Taking SMX and TMP, the most frequently co-occurred antibiotics in rivers (Table S3), for geographical distribution analysis, their concentrations were diverse in river waters across various countries (Figure 3A, 3B, and S5), and the median concentrations ranged ND–4360 ng/L for SMX and ND–1200 ng/L for TMP (Table S5), respectively. The hotspots of antibiotic pollution were found in rivers of the following countries such as Mozambique (MOZ), Uganda (UGA), Nigeria (NGA), Kenya (KEN), South Africa (ZAF), India (IND), and Mexico (MEX) (Figure 3A and 3B), mostly in low income countries (LICs) and lower-middle income countries (LMICs) (Figure 3C) with higher population density (Figure 3D). The high concentrations of SMX and TMP in African countries were likely attributed to the direct discharge of untreated or unregulated wastewaters [63,65]. India, as a member of emerging economies in Asia with gross national income (GNI) per capita of 1920 current US$ and population density of 464 person/km^2, leads the LMICs consumers of antibiotics with 6.5 billion DDDs in 2015 [3].

The significant difference in the rivers for the concentrations of SMX and TMP in different countries seemed relevant to national income levels in terms of World Bank country classification, following the order

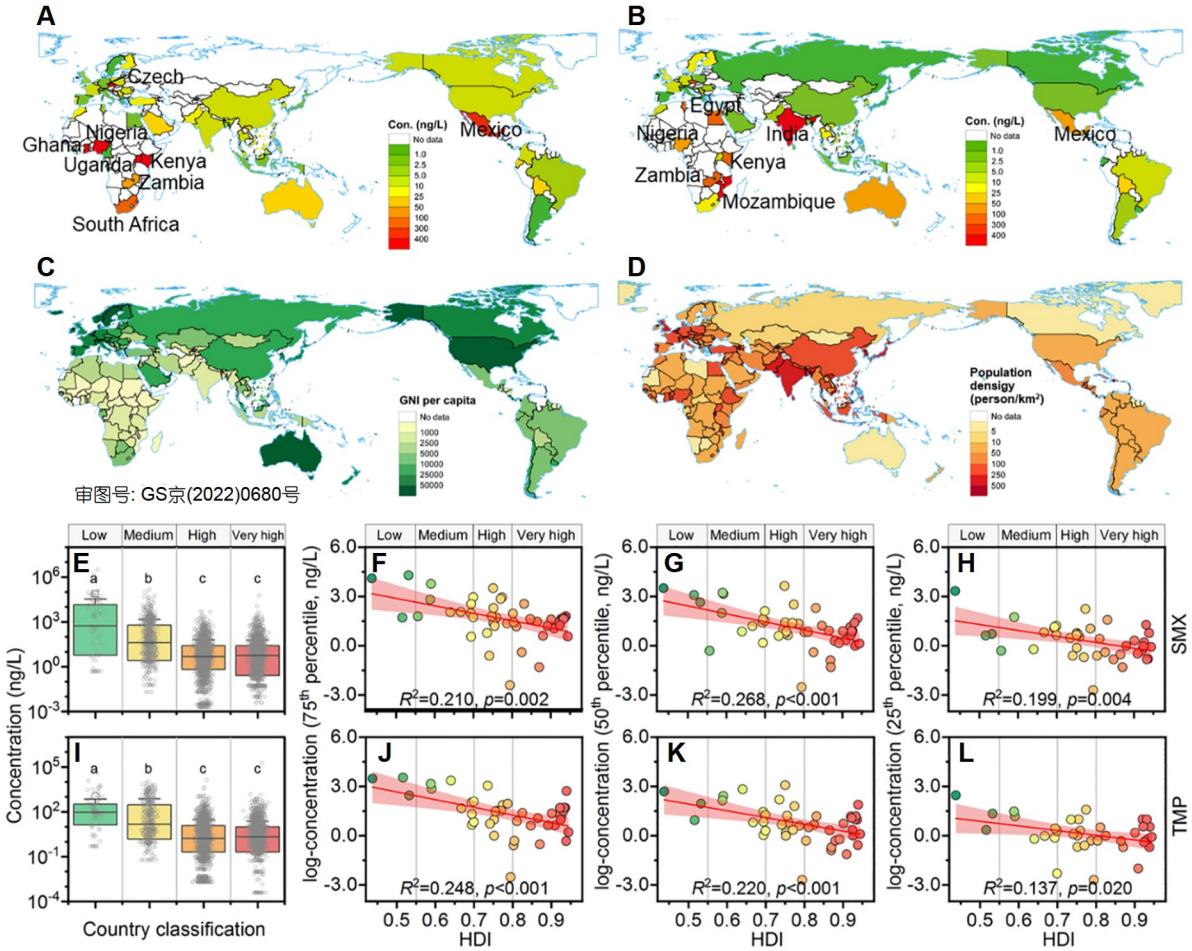

Figure 3 Geographic distribution of two most studied antibiotics and their relation with natural and socioeconomic variables. Geographic distribution of SMX (A) and TMP (B) concentrations in river waters from different countries. Gross national income (GNI) per capita (C) and population densities (D) of different countries. Comparison of SMX (E) and TMP (I) concentrations in countries of different classification based on human development index (HDI). Linear relationships between the characteristic concentrations (75th, 50th, and 25th percentiles) of SMX (F−H) and TMP (J−L) in river water and HDI.

of LICs≈LMICs>upper-middle income countries (UMICs)≈high income countries (HICs) (Figure S6). The high antibiotic concentrations in LICs and LMICs were associated with less regulated access to antibiotics and limited wastewater treatment infrastructures [33]. Low concentrations of SMX and TMP were found in HICs, despite their higher antibiotic consumption rate (DDDs per 1000 inhabitants per day) [3], possibly due to increased capacity and efficiency of wastewater treatment facilities as well as management of antibiotic therapy. Antibiotic consumption may increase in LICs and LMICs, where access to antibiotics is rising [34]. Consequently, antibiotic pollution in less developed countries will be further aggravated.

Compared with antibiotics in water, no significant difference in the concentrations of SMX and TMP was observed in sediment from the selected countries (with available data number >10 in each country) (P>0.05, Figure S7). Relatively low concentrations of SMX (median ND–0.33 ng/g) and TMP (ND–1.08 ng/g) were witnessed (Figure S7) in these countries presumably because of their low affinity to sediment [11], though only eight countries (USA, Spain, Poland, Italy, China, Brazil, Viet Nam, and Kenya) were covered due to the

limitation of data access for antibiotics in sediment.

Distribution of antibiotic concentration in representative river basins

Seven river basins were chosen for further comparison of antibiotic pollution levels, including those from Asia (Yangtze River, Yellow River, Pearl River, and Ganges River), Europe (Danube River and Rhine River), and North America (Mississippi River) with the large watershed area, dense population, and intensified anthropogenic interference (Table S6). We found that SMX was the highest in the Ganges River ($P<0.05$, Figure S8A), with the median and 75th percentile values of 10.9 and 390 ng/L, respectively. Similarly, TMP was also higher in the Ganges River (median 431 ng/L, 75th percentile 1687 ng/L) than in other rivers, e.g., the Yangtze River, Pearl River, and Mississippi River (Figure S8B). About 37.5% of SMX and 50.0% of TMP samples exhibited high concentrations (>100 ng/L) in the Ganges, much more frequently than those detected in other rivers (Figure S8C and S8D). Higher SMX and TMP occurred in the Ganges largely associated with the highest population density (425 person/km^2) (Table S6) as well as the discharge of agricultural, domestic, and industrial wastewater without treatment in the basin [67]. Comparable median concentrations (4.80–36.4 ng/L) of SMX were observed in other river basins except the Ganges (Figure S8A). As for TMP, the Yellow River displayed the highest concentration variability (six orders of magnitude) with a median of 12.6 ng/L, while the other rivers showed comparable levels (except the Ganges) with median values of 0.72–4.37 ng/L (Figure S8B). The relatively low concentrations of SMX and TMP in the Yangtze River were ascribed to relatively high water flow (average 3.0×10^4 m^3/s) [11] and effective control of wastewater under heavily populated pressure (267 person/km^2, Table S6) in the basin.

Driving factors

The geographical distribution pattern of antibiotic concentration in rivers across different countries can partially be explained by socioeconomic factors [33], such as GNI index, population, median age, local unemployment, death rate, and human health [33]. In addition, the climate factors, e.g., precipitation and temperature, may influence the antibiotic concentration by changing water flow and affecting the usage and biotransformation of antibiotics [11–13].

Factor identification

To delineate the factors determining the environmental pollution of antibiotics across different countries, distance-based redundancy analysis (dbRDA) was carried out, in which two climate variables (i.e., average temperature and average annual precipitation) and five socioeconomic variables (i.e., GNI, population density, life expectancy, access to education measured by expected years of schooling of children at school-entry age and mean years of schooling of the adult population, and unemployment rate) with variance inflation factors less than 10 were selected. It was found that antibiotic pollution in different countries was negatively related to GNI index, life expectancy, and access to education (Figure S9A), but was poorly associated with population density, unemployment rate, and average annual precipitation. The average

annual temperature seems to have apparent effect on antibiotic concentrations, but an alternative interpretation could be that most LICs with high antibiotic concentrations are located in hotter areas.

Variance partitioning analysis (VPA) unveiled that the socioeconomic variables accounted for 66% of the total variation in antibiotic concentrations, while the natural variables only explained 2% of the total variation in antibiotic pollution (Figure S9B). This reveals that socioeconomic variables were the main drivers of antibiotic pollution rather than climate variables. It is reasonable that developed countries usually have better water quality than less developed countries. Statistical analysis (Figure S9C and S9D) revealed the negative relationships between antibiotic concentration in river water and socioeconomic variables. Particularly, the median concentrations of SMX and TMP were significantly correlated with GNI ($P<0.01$), life expectancy ($P<0.01$), and total years of schooling of the adult population (TY, $P<0.05$) (Figure S9C and S9D). The population should have been an influencing factor for pharmaceutical pollution in the world's rivers [33], but the positive relation between them seemed more likely occurred in LICs and LMICs rather than in HICs. For instance, greater population density in Japan (345 person/km^2), Germany (238 person/km^2), the United Kingdom (278 person/km^2), Switzerland (219 person/km^2), and Italy (200 person/km^2) did not correspond to a high concentration of antibiotics (Figure 3A–3D).

Human development index

GNI, life expectancy, and access to education are indicators to measure human development, which are three key dimensions for the human development index (HDI). The concentrations of SMX and TMP in different countries were related to the HDI ranking, and they decreased with increasing HDI ranking in the order of low>medium>high≈very high (Figure 3E and 3I). In particular, the characteristic concentrations of SMX and TMP (75th, 50th, and 25th percentiles) in water were strongly and negatively correlated with HDI in different countries (Figure 3F–3L, $P<0.05$). A recent study [33] also found socioeconomics and human health are key predictors of pharmaceutical pollution. The countries with high GNI typically have higher connectivity to waste and wastewater treatment facilities, more advanced treatment systems, and better regulation of antibiotic use, thus resulting in relatively lower concentrations of antibiotics in water. A good education helps us to use antibiotics judiciously, leading to low levels of antibiotic pollution. HDI, encompassing economic, health, and education, is an integrated index reflecting the socioeconomic developmental levels. The present result suggests that HDI may be used as an indicator for prediction of antibiotic pollution and prioritization of locations for antibiotic risk management, which needs to be verified by further studies.

Risk assessment

The antibiotics may pose potential ecological risks to aquatic organisms and human health. Pharmaceutical analysis indicated that antibiotic concentration was in the range known to cause acute or chronic toxicity in aquatic systems [16]. Here, we estimated the risks of antibiotics in rivers from the five continents, using risk quotient (RQ) on the basis of the chronic toxicity to fish, daphnids, and green algae [68] and non-cancer risk to humans [69,70], respectively.

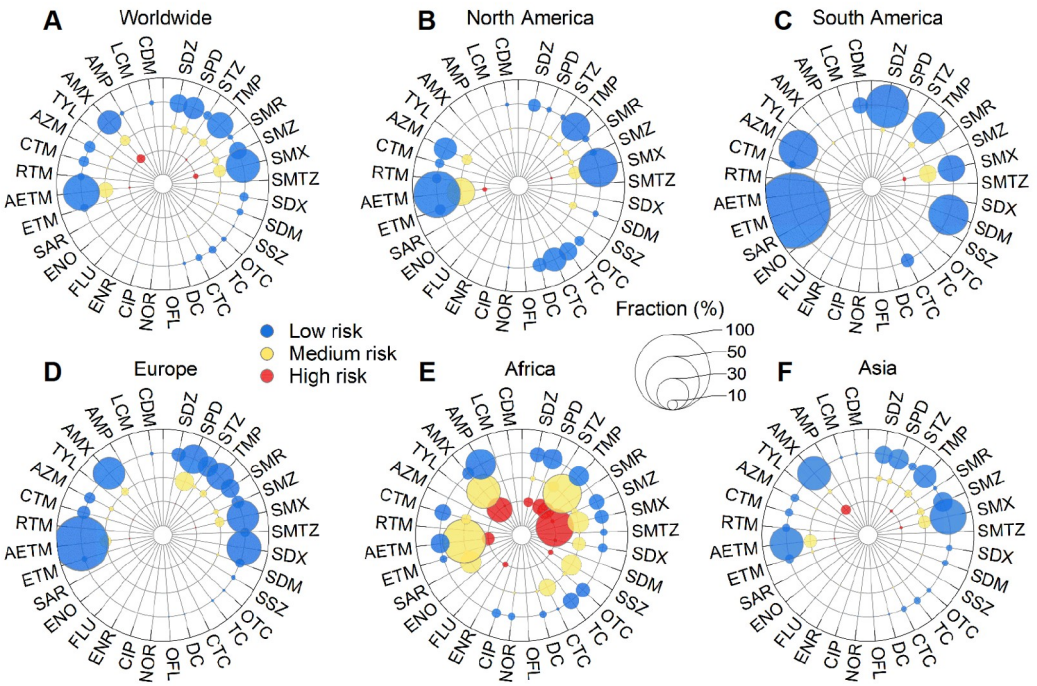

Figure 4 Potential ecological risks of 32 representative antibiotics in rivers from different regions. Fractions of different risk levels for 32 representative antibiotics in rivers of the globe (A), North America (B), South America (C), Europe (D), Africa (E), and Asia (F).

Ecological risk

Antibiotics in many sampling sites exhibited ecological risks at different levels to aquatic organisms (Figure S10). Figure 4 demonstrated diverse ecological risks among antibiotics in different regions, in which SAs, MLs, and β-Ls exhibited higher risks to aquatic organisms, while TCs, QNs, and LMs generally posed insignificant risks (Figure 4A–4F, S10 and S11). At global scale (Figure 4A), the individual antibiotics showing higher frequency of risks included AETM (50.4%), SMX (48.1%), AMX (40.4%), and TMP (33.8%). At regional scale, the highest risk potentials of antibiotics were found in African water (Figure 4E), with a much higher frequency of risks (66.3−71.2%) induced by AETM, SMX, AMX, and TMP.

Human health risk

The non-cancer risk from the representative antibiotics in water was negligible (RQ_H<1) except for one OTC point in Asia and two SMX points in Africa (Figure S12). Hence, human health risks were not considered in the screening of priority antibiotics.

Prioritization of antibiotics

Prioritization scheme

The weighted frequency of RQ (WFRQ) for a specific antibiotic was proposed as a risk surrogate for the

prioritization of antibiotics, which was calculated using the method modified from Yang *et al*. [71] (eq. (1)).

$$\mathrm{WFRQ} = \sum_{i=1}^{4} F_x W_x, \tag{1}$$

where F_x is the fraction of RQ data numbers of rank class x in the total RQ numbers for a specific antibiotic (i.e., the frequency of rank class x), and x was assigned of 1 for high risk (RQ>1), 2 for medium risk (0.1<RQ<1), 3 for low risk (0.01<RQ<0.1), or 4 for insignificant risk (RQ<0.01). W_x is the weighting index, which was assigned of 1 for high, 0.5 for medium, 0.25 for low, or 0 for insignificant risks, respectively [71]. F_x herein was the frequency of rank class x rather than the number of data. This excluded the influence of data number on the antibiotic prioritization, and facilitated the comparison of WFRQ values for various antibiotics in different regions. Moreover, the frequency could reflect the overall occurrence of antibiotics and avoid misleading by an unconscious "false" detection. This method is particularly appropriate for the vast dataset. For an adequate evaluation of the potential risks of each antibiotic, WFRQ was calculated only if the antibiotic concentration dataset comprised more than 50 records.

Antibiotic prioritization at a global level

The WFRQ values were calculated according to our proposed approach (eq. (1)), and 78 antibiotics had ecological risks to the aquatic organisms with WFRQ values of 0.001–0.188 in the world's rivers (Figure 5B). The rank list indicated the antibiotics with different priority levels for global attention. Remarkably, 22 SAs, 13 TCs, 15 QNs, 9 MLs, 10 β-Ls, and 9 others were listed in the priority antibiotics (Figure 5B). Thereinto, AMX, SMX, AETM, TMP, and sulfapyridine (SPD) were the top five priority antibiotics in global river water. AMX is a widely used broad-spectrum antibiotic in human and veterinary medicine for the treatment of respiratory, urinary, and skin bacterial infection, which was also identified in the previous prioritization studies [72–75]. AMX is even an over-the-counter drug, which could be supplied to patients without prescription in some African countries [76]. SMX and TMP were previously identified as the priority antibiotics in surface water in China [11,37–39] and France [75] due to their common usage and high persistence in water [77]. AETM, as a typical degradation product of ETM [78], was identified as high priority in the previous studies [11,79]. SPD is commonly used as veterinary medicine, which was ranked as a medium priority antibiotic in the aquatic environment of China [39].

Among different classes of antibiotics, SAs represented the largest share (44.6%) of the total WFRQ values (Figure S13), which was approximately threefold that of MLs (15.8%), β-Ls (13.6%), and TCs (14.2%). QNs or other antibiotics accounted for less than 8% of the WFRQ values. β-Ls are the most consumed antibiotics by humans, accounting for 59% of the global antibiotic consumption [3]. However, the detection frequency of β-Ls in water was usually lower due to their quick attenuation by hydrolysis catalyzed by metal ions [80–82]. Therefore, β-Ls generally posed lower risks in water except for AMX. TCs are the top veterinary antibiotics in food animals worldwide [83], while QNs (27%) and TCs (20%) are the most commonly used antibiotics in aquaculture globally [34]. However, the sorption to sediment greatly contributed to the attenuation of TCs, QNs, and MLs in water [11,84], as revealed by their higher K_{oc} values (Figure S14A and Table S2). Apart from adsorption, photodegradation was found to be a dominant attenuation process for QNs and TCs (Figure S14B) rather than biodegradation and hydrolysis in river systems [85].

The persistence of SAs in river water could result from their resistance to photolysis due to their chemical stability [86]. Compared with other classes of antibiotics, SAs are resistant to photolysis with relatively high E_{gap} values (Figure S14B), though they present comparably high hydrolysis (Figure S14C) and biodegradation potentials (Figure S14D). Notably, SAs are not the dominant class of antibiotics used in human or animals (Figure S14F and Table S7), sharing only 5% of the total usage of antibiotics in China [4], less than 5% of the antibiotic usage of food animals in USA, and less than 3% of the total use in human medicine and 10.5% of the total use in food-producing animals in the European countries [20]. However, SAs demonstrated high concentrations in water (Figure 2) as well as higher risk potentials (Figure S14E) associated with their mobility [84,85] and high toxicity to aquatic organims (Figure S14E).

Antibiotic prioritization at a continental level

Antibiotics in surface water were ranked in different continents based on the WFRQ values. The pie charts showed the contributions of WFRQ values from different classes of antibiotics (Figure 5A). The largest proportion was SAs, followed by MLs, TCs or β-Ls, others, and QNs, suggesting SAs as the antibiotic class of the most concern. In addition, SAs displayed the highest numbers in the prioritized list (3–19), followed by MLs (2–9) and TCs (1–11) (Figure S15A and Table S8). This is consistent with the high detection frequencies and occurrence levels of SAs. On the other hand, the accumulative WFRQ values of antibiotics followed the order of Africa>Asia>Europe>North America>South America, indicating Africa might be the hotspot for the pollution control and risk management of antibiotics. The lowest accumulative WFRQ value of antibiotics for South America was mainly ascribed to its least number of prioritized antibiotics (Figure 5D).

The number of investigated priority antibiotics in surface water showed significant geographical difference in North America (22), South America (10), Europe (33), Africa (19), and Aisa (65) (Figure 5C–5G and S16). The least number of priority antibiotics for South America was likely due to its limited records in the antibiotic dataset. It is worth mentioning that SMX and TMP, characterized with their higher persistence [84,85] and long history in use [87], were listed in the top five priority in surface water from all the five continents. Moreover, AMX was also identified as a high priority in the investigated rivers in Africa, Asia, Europe, and South America (Figure S17), while SMZ appeared in the list of the top 10 priority antibiotics in all continents except South America (Figure S17). AETM exhibited relatively higher priority in Africa, Europe, and Asia (Figure S17), and AZM was ranked 2nd, 4th, and 10th in North America (Figure 5C), South America (Figure 5D), and Europe (Figure 5E). Another two priority antibiotics were SPD, mostly observed in rivers of Asia, Europe, and Africa, as well as sulfadiazine (SDZ) which received increasing attention in Asia, North America, and South America (Figure S17).

Antibiotic prioritization at a country level

Considering the data availability, we focused on screening the priority antibiotics (types) in rivers from China (59), USA (19), Spain (17), and Brazil (8) (Figure S15B and Figure S18). The dataset contained much more antibiotic records in China than the rest part of the world, leading to a much greater number of the investigated priority antibiotics therein. However, the WFRQ values of investigated priority antibiotics in

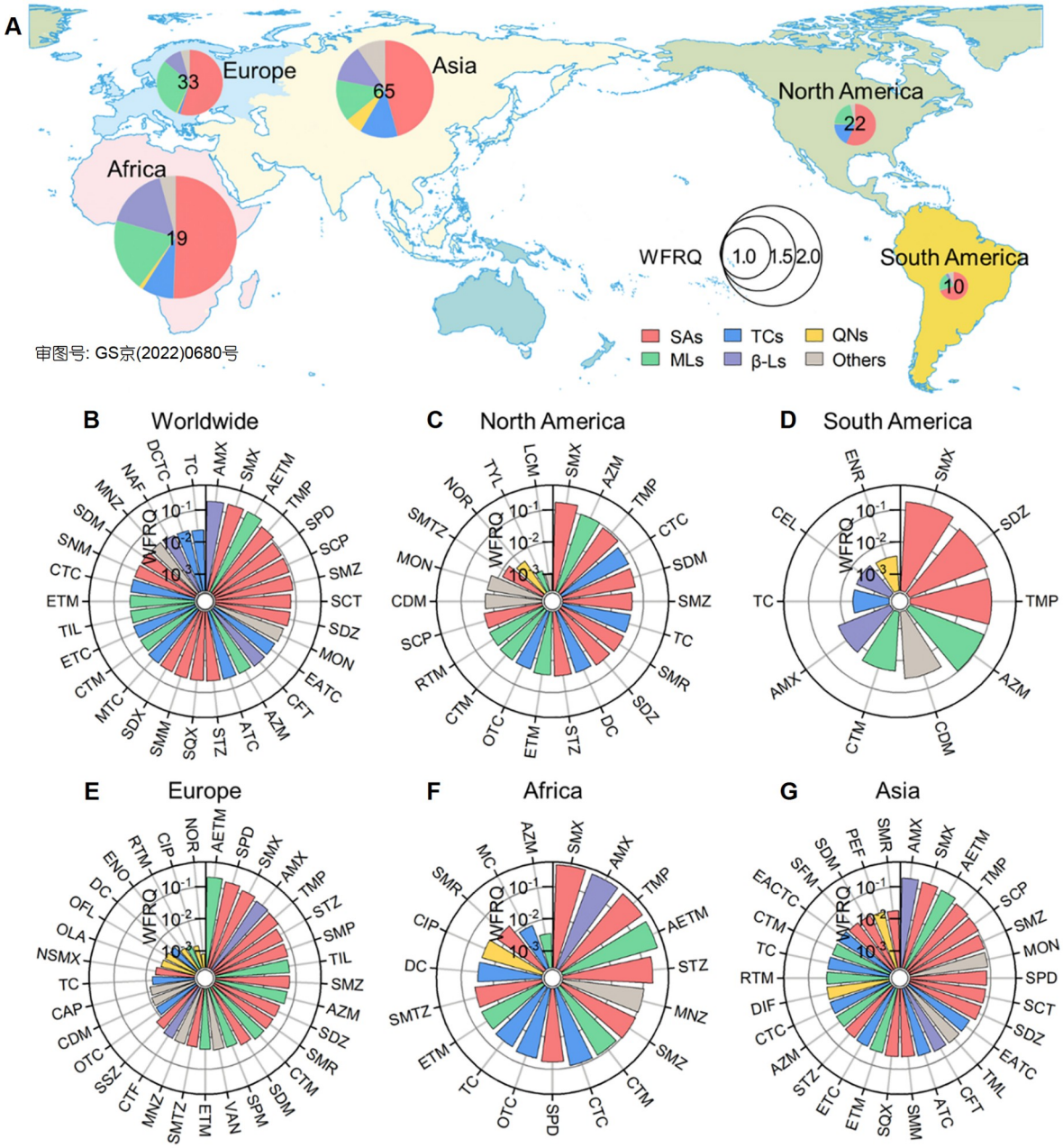

Figure 5 Rank orders of the prioritized antibiotics at global and regional levels. The accumulative WFRQ for each of five continents (A) (The chart size indicates the accumulative WFRQ, and numbers on the pie chart suggest the number of prioritized antibiotics in each continent). The rank order of the prioritized antibiotics at a global level (top 30 antibiotics) (B). Rank orders of the prioritized antibiotics in North America (C), South America (D), Europe (E), Africa (F), and Asia (top 30 antibiotics) (G).

China were relatively low, with a median of 0.014, which was the lowest among the four representative countries (Figure S19). This indicates the low risk level and frequency of antibiotics in China despite the large number of priority antibiotics. The highest WFRQ value (median 0.072) in Brazil seemed not statistically different with that in other countries (Figure S19). SMX and TMP were ranked top five in all these countries, suggesting that poriority should be given to their pollution control and risk management.

Recommendations for antibiotic management

In the long run, reducing antibiotic consumption is most effective to mitigate the global antibiotic pollution. Therefore, a comprehensive global framework for all stakeholders targeting reduction of antibiotic usage is urgently required [88]. Without loss of generality, we proposed six separate domains for global governance by stressing the most prominent aspects (Figure 6A).

First, life cycle management of antibiotics at different systems is proposed as a basic spirit, which requires close multisectoral (e.g., sectors on the environment, human health, animal health, industry, and food safety), regional, and international collaborations [89]. For such a purpose, understanding the whole process of antibiotics from production, sale, consumption, discharge, and pathway is of primary importance [90,91]. Second, a global surveillance system across various basins and countries should be established. Many countries have set up the National Action Plan against antimicrobial resistance or reducing antibiotic use [92–95] under the umbrella of the Global Action Plan established by the World Health Organization [24]. However, most of the national action plans lack the aspect of monitoring antibiotic residues in the environment [24]. Despite the vast antibiotic data surveyed in rivers worldwide, the geographic coverage of data points is far insufficient, particularly in less developed countries in Africa and South America, and the countries in North and Southeast Asia (Figure 1A and Figure 6B). According to our prioritization protocol, AMX, SMX, AETM, TMP, and SPD should be the top five priority antibiotics needing more surveys. Third, awareness strengthening and knowledge renewing on optimal antibiotic use and proper disposal of expired medicine are critical for appropriate antibiotic use in human and animals. Now, the development of stewardship programs is ongoing in many LICs and MICs (Figure 6B). From the perspective of prevention, the education of the general community, veterinary, medical, and other health related professionals about the prudent use of antibiotics are essential [19,20]. Besides, consumers should be aware to the serious consequences related to inappropriate use of antibiotics through education and communication. Fourth, infrastructure and healthcare need to be strengthened in less developed areas. Currently, the geographical hotspots of antibiotic pollution prevailed in LICs and MICs such as Mozambique, Uganda, Nigeria, Kenya, and South Africa in Africa, India in Asia, and Mexico in North America (Figure 3A and 3B). These countries are facing

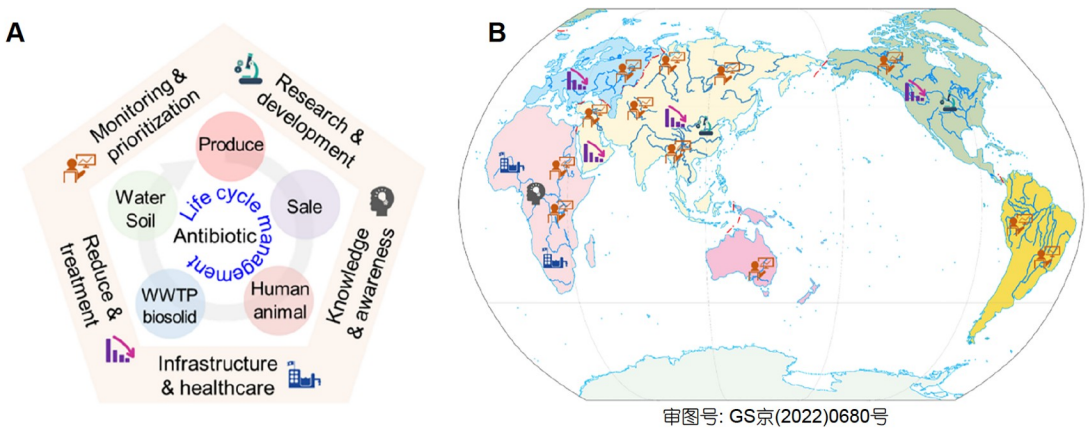

Figure 6 Countermeasures for antibiotic management (A) and the prioritized region-specific strategies for different continents (B) (The same symbols in A and B represent the same countermeasures).

great challenges of lacking basic infrastructure and equipment and shortage of healthcare professionals and personnel [96], requiring improvement of sanitation, access to clean water, increase of health expenditure, and infection control and prevention (Figure 6B) [91]. Fifth, differentiated measures should be used in different areas according to their existing antibiotic pollution problems and socioeconomic developmental levels. In HICs, reducing antibiotic use should still be the priority considering their high antibiotic consumption rate (Figure 6B), despite the relatively low antibiotic concentrations in rivers therein. In LICs and MICs where expanding essential access to medicines, great efforts should be paid on reducing inappropriate antibiotic use. In addition, antibiotics used for food animals are responsible for 73% of antimicrobials globally [83], and efforts on ban of antibiotics as a growth promoter in animal feed are needed to be strengthened continuously worldwide. Meanwhile, proper treatments of animal waste and household, hospital, and drug manufacturer wastewater are also urgent tasks in the coming years [14,15]. Lastly, collaborative research is highly necessary in the campaign of reducing antibiotic pollution [97], which greatly promotes the development of new antibiotics or alternatives [26,98] and advances technologies fundamentally limiting the environmental burden of antibiotics [1,71].

Implications and perspectives

By establishing a global dataset on antibiotics, we identified the hotspots of polluted rivers in terms of the most representative antibiotics (SMX and TMP) in 56 countries, which provided essential information for location prioritization and trend prediction of antibiotic pollution. Meanwhile, negative linear relationships between HDI and antibiotic levels were revealed. Future efforts should be made to enrich the dataset with greater coverage of antibiotic types and rivers across more countries. Due to the limitation of the *in-situ* monitoring data, predictive models should be developed as a supplementary tool to link the antibiotic levels with the socioeconomic variables and to foresee the trend in antibiotic pollution under different scenarios.

In the present study, we developed a risk-based prioritization protocol to identify which antibiotics should be of particular concern in specific river basins. Since the type and data number of antibiotics varied significantly across regions, the prioritization results are highly dependent on the availability of monitoring data of antibiotics. Moreover, the risk was evaluated based on the toxicity data predicted by *in-silico* tools, which might not exactly represent the *in vivo* toxicity to aquatic ecosystems. The ecological risk of antibiotics to aquatic organisms such as green algae, daphnids, and fish would be unable to simulate their potential risks for antimicrobial resistance selection. Future studies are highly needed to remedy these insufficiencies.

Increasing concerns about antibiotic residues in the environment include a selection of antibiotic resistance [99], dissemination of ARGs [100], promotion of genetic transformation [101], and alteration of the population dynamics of microorganism in natural environments [23,102]. These issues are possibly relevant to emergence of unknown antibiotic-resistant pathogens [23,28,103,104]. With the development of new efficacious antibiotics, the genetic (including resistome) diversity would increase as well in facing the antibiotic and other chemical diversity. Besides the removing technologies of ARGs, the long-term impacts of environmental antibiotics on microbial communities (particularly archaea, fungi, and pathogens), microbial metabolic diversity, and biogeochemical cycling of nitrogen or carbon would be important topics in future studies.

Methodology

Data collection

We searched the occurrence of antibiotics in surface water and sediment worldwide from the Web of Science, using the terms "antibiotics/pharmaceutical/PPCPs/antimicrobials" and "water/river/lake/sediment" up to 31 August 2021. The records were screened by deleting duplicates and irrelevant ones and supplemented by checking the article's references. Finally, 606 articles (Table S1) identifying antibiotics in surface water and sediment were retained and used to constitute a global atlas, including the document's year, the targert analytes, sampling period, locations of the monitoring sites, and antibiotic concentrations.

Data on GNI per capita and population density were extracted from World Bank open data. Data on life expectancy, expected years of schooling of children at school-entry age, mean years of schooling of the adult population, HDI, unemployment rate, and the meat productions of aquaculture, beef and buffalo, pig, and poultry were obtained from the website of https://ourworldindata.org/. The climate data of temperature and precipitation (mm) were extracted from https://www.worldclim.org/data/worldclim21.html.

Data analysis

The concentration values of antibiotics in surface water and sediment from individual sampling sites were collected from the publications to generate a global antibiotic concentration dataset. The latitude and longitude of the sampling sites were extracted by Google Earth if they were not given in the articles. The concentrations of antibiotics in graphs were digitized using GetData Graph Digitizer (v2.26) when data values were not given in the articles. The concentrations of antibiotics below the limit of detection (LOD) or limit of quantification (LOQ) were entered as a half of LOD or LOQ for statistical analysis [11]. If the reported LOD or LOQ was above 20 or 20 ng/g, the antibiotic concentrations below LOD or LOQ were excluded in statistical analysis. Locations of monitoring sites were visualized in ArcGIS (v10.8.1). Network analysis was performed in Gephi (v0.9.2). Box plots, violin plot, and polar diagrams were performed in Origin 2020b. Heatmaps were plotted by using R software (v4.3.1).

Predicted properties of antibiotics

The sorption, biodegradation, and hydrolysis potentials of antibiotics were predicted by VEGA (v1.2.0) [105]. The direct photolysis potential of each antibiotic was estimated by the energy gap (E_{gap}) between the lowest unoccupied molecular orbital (LUMO) and the highest occupied molecular orbital (HOMO) [106]. The frontier orbital energies of antibiotics were optimized at the B3LYP level in conjunction with the 6-31g (d,p) basis set [107] using the Gaussian 16 C.01 software [108]. A solvation model based on density (SMD) was used to simulate the state of neutral molecules in water.

Identification of driving factors

Using R program (v3.6.3), we conducted dbRDA to delineate the factors influencing environmental pollution of antibiotics, in which parameters with variance inflation factors lower than 10 were selected. In Table S9,

socioeconomic and climate variables used for dbRDA are provided for different countries. VPA based on canonical correspondence analysis was performed to decouple the pure and joint effects of natural and socioeconomic factors on antibiotic pollution. Spearman correlation analysis was carried out to investigate the relationships between antibiotic concentration and socioeconomic variables.

Risk assessment of antibiotics

The ecological risk of each antibiotic was calculated using the RQ method [77] according to eq. (2).

$$RQ = MEC/PNEC, \tag{2}$$

where MEC represents the measured environmental concentration of each antibiotic, and PNEC represents its predicted no effect concentration, which was calculated by dividing the chronic toxicity data with an assessment factor of 100 [77]. The chronic toxicity of antibiotics to fish, daphnids, and green algae was predicted using ECOSAR software (v2.0) and the lowest chronic toxicity to the three trophic levels of organisms was used to simulate a worst case scenario. The levels of ecological risk could be divided into insignificant (RQ<0.01), low (0.01<RQ<0.1), medium (0.1<RQ<1), and high (RQ>1) risks.

Non-cancer risk, represented by the risk quotient for a specific antibiotic (RQ_H), was calculated according to eq. (3) [69]:

$$RQ_H = CDI/RfD, \tag{3}$$

where RfD (mg/(kg d)) is the chronic reference dose for a specific antibiotic. The RfD values were predicted by the conditional toxicity value software (http://toxvalue.org) and shown in Table S2. CDI (chronic daily intake, mg/(kg d)) was calculated according to eq. (4) [69]:

$$CDI=(C \times IR \times EF \times ED) / (BW \times AT \times 10^3), \tag{4}$$

where C (mg/L) is the concentration of an assessed antibiotic. Considering that the removal efficiencies of different antibiotics vary significantly in drinking water treatment plants with various treatment processes from different regions and countries, it is extremely hard to specify a unified removal efficiency for each antibiotic on a global scale. Therefore, we took an average value of 46.8% for simplification [77], and C is the 53.2% of the identified concentration for a specific antibiotic in this study. IR (L/d) is the ingestion rate of drinking water, EF (days/year) is the exposure frequency, ED (a, year) is the exposure duration, BW (kg) is the body weight, and AT (d) is the average life time. The parameters used in eq. (4) were given in Table S10 [70].

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Author contributions

W.S., J.N., and S.L. designed the work. S.L., Y.L., Y.W., Y.Z., and Q.S. performed the bibliometric analysis. J.H., D.J., X.Y., D.Q., M.T., Y.L., F.K., L.C., Y.A., and Y.W. collected data and carried out relevant analyses. J.G. and X.L. made calculations and derived the toxicity information of antibiotics. S.L. and W.S. wrote the manuscript with help of J.N.. All authors have read and improved the manuscript.

Conflict of interest

The authors declare that they have no conflict of interest.

Supplementary information

The supporting information is available online at https://doi.org/10.1360/nso/20220029. The supporting materials are published as submitted, without typesetting or editing. The responsibility for scientific accuracy and content remains entirely with the authors.

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