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Review

Global antibiotic hotspots and risks: A One Health assessment

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A B S T R A C T

Antibiotics are increasingly prevalent in global environments, driving antimicrobial resistance and disrupting microbial cycling. These impacts pose threats to human, animal, and environmental health. Therefore, addressing this emergent issue necessitates a One Health framework that integrates these interconnected dimensions. Here we systematically review 137 antibiotics across diverse global environmental compartments. We find that sulfonamides, macrolides, quinolones, and tetracyclines are globally ubiquitous, particularly prevalent in Asia and Africa, whereas β-lactams dominates in Europe. Hierarchical clustering revealed ten priority antibiotics in liquid phases and eight in solid phases requiring urgent attention. Regional analysis indicated the highest antibiotic concentrations within wastewater treatment plant liquids in the Americas and surface waters in Africa, with generally lower levels detected in Asia and Europe. Utilizing a One Health assessment framework, we integrated Predicted No-Effect Concentrations for antibiotic resistance selection ($PNEC_{RS}$) relevant to human and animal health with Minimum Inhibitory Concentrations (MICs) affecting microbial nitrogen cycling processes. Risk assessment highlighted wastewater treatment plant liquids (20% average exceedance) and animal manure (44% average exceedance) as the most critical compartments. Africa exhibited the highest overall risk, averaging a 53% exceedance rate. Notably, ciprofloxacin and ofloxacin in liquid phases, as well as enrofloxacin and norfloxacin in solid phases, emerged as antibiotics posing significant One Health risks. This study advances our understanding of antibiotic distribution globally, offering a foundation for targeted interventions to mitigate antibiotic-related risks across human, animal, and environmental health sectors.

1. Introduction

Antibiotic pollution and antimicrobial resistance have emerged as pressing environmental health concerns. For decades, antibiotics have been extensively used in medicine and agriculture to treat human and animal diseases caused by pathogenic bacteria [1–4]. However, there has been a sharp rise in global antibiotic consumption due to increasing population, improved economic conditions, and the use of growth-promoting drugs in livestock farming, with the COVID-19 pandemic potentially expanding the usage further [5–7]. For instance, the use of human antibiotics increased by 65% from 2000 to 2015, and it has been projected to rise by 200% by 2030 [8,9]. Furthermore, the global use of veterinary antibiotics was estimated at 76,704 tons in 2018, with a projected increase of 67% by 2030, reaching 105,596 tons [10]. Notably, a significant portion (30–90%) of the active ingredients in antibiotics used by organisms is excreted through feces and urine into the environment [11,12]. The presence of antibiotics in the environment induces the development of antibiotic resistance genes

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(ARGs), which can transfer from environmental bacteria to pathogens and threaten human and animal health, thus creating a critical public health issue [13–15]. In 2019, antimicrobial resistance (AMR) was associated with 4.95 million deaths worldwide [16]. Deadlier pathogens might appear if no actions are taken to control antibiotic use [16].

Antibiotics facilitate the development of AMR through their effect on nitrogen cycling processes [17,18]. Active nitrogen and antibiotics often coexist in natural environments [19,20]. Even at low concentrations, antibiotics can exert selective pressure on bacterial communities by disrupting biogeochemical cycles, such as nitrification, denitrification, anaerobic ammonium oxidation, and dissimilatory nitrate reduction to ammonium in the nitrogen cycle [21–23]. These disruptions may impair functional genes and inhibit the activity of microorganisms in the nitrogen cycle, leading to increased nitrous oxide emissions, global warming, and stratospheric ozone depletion [24–27]. Moreover, various biogeochemical processes that pose a threat to humans, animals, and ecosystems are also influenced by antibiotics [17,18,28].

In view of these circumstances, it is crucial to understand the role of antibiotics in the environment and AMR dissemination from One Health's perspective [29,30]. Notably, One Health aims to optimize the health of humans, animals, and ecosystems using a holistic, balanced, and systematic strategy [31]. It recognizes the intrinsic connection and coexistence between human, animal, and environmental health. As a result, it calls for close communication and collaboration among relevant sectors to collectively build and promote a sustainable and healthy future [32]. In this context, it must be noted that most existing studies examining the risks posed by ARGs from antibiotics in a specific environmental system or organism have been conducted without considering the organisms and environmental systems as an integrated whole, thereby overlooking their deep interconnections [3,33–36]. This limitation highlights the need for a more comprehensive One Heath approach to understanding the complex impacts of antibiotics on the environment.

Assessment of antibiotics in terms of the One Health approach necessitates a comprehensive dataset comprising details of their impacts on humans, animals, and ecosystems. We first established a database of peer-reviewed papers published between 2012 and 2022 to address this need. We then systematically analyzed the data with the objectives of (1) elucidating the global distribution patterns and co-occurrence of antibiotics, (2) analyzing detection frequencies and environmental residue concentrations of antibiotics across different continents and environmental compartments, (3) identifying priority antibiotics in the global environment, (4) evaluating the probabilistic risk of resistance to priority antibiotics and their risk to microorganisms involved in the nitrogen cycle, and (5) revealing the nature of global antibiotic pollution from a One Health perspective.

2. Methodology

2.1. The dataset

The literature reviewed in this study was retrieved from the Web of Science (https://webofscience.clarivate.cn/). Since antibiotics from major pollution sources ultimately enter either the liquid or solid phase, we conducted thematic searches using keywords such as “antibiotics” and those related to specific environmental compartments, including “wastewater treatment plant,” “sludge,” “animal farm,” “manure,” “surface water,” “sediment,” “soil,” “groundwater,” and “aquifer.” Compartments such as landfills were categorized as point source pollution since the leachate from landfills can contaminate the surrounding soil and groundwater [37]. Consequently, data related to landfills were classified as soil or groundwater to assess their environmental impacts more accurately. The environmental compartments mentioned above are present in multiple critical pathways related to human, animal, and ecological health, thus offering comprehensive data to support research within the One Health framework. We only selected publications in peer-reviewed journals written in English that include quality assurance (QA) and quality control (QC) in their processes. Furthermore, articles related to ARGs were manually excluded, retaining only those that reported antibiotic concentration data. Ultimately, a total of 253 articles published between 2012 and 2022 covering 46 countries were identified globally (Supplementary Material Fig. S1–S2).

The datasets considered in the reviewed literature include detailed information on antibiotic names, classifications, environmental compartments, countries, geographic coordinates (latitude and longitude), and references. We also recorded the maximum, minimum, mean, and median concentrations of each antibiotic. In the case of studies where the data underlying the figures were not clearly reported in the text, the data were extracted using WebPlotDigitizer 4.6 [38]. Furthermore, antibiotic concentration values falling below the method detection limit (MDL) were replaced with $MDL/\sqrt{2}$ [39]. Moreover, the unit for each data parameter was unified. Concentrations in surface water, groundwater, influents and effluents from wastewater treatment plants (wastewater from WWTPs), and animal wastewater from farms were converted to nanograms per liter (ng L^{-1}). For soil, sediment, sludge from wastewater treatment plants (WWTP sludge), and farm animal manure, the concentrations were converted to micrograms per kilogram dry weight (μg per kg dry weight). The resulting dataset comprised 431,441 records covering 137 antibiotics in eight environmental compartments worldwide. The 137 antibiotics were further grouped into seven classes based on their chemical structures—sulfonamides (including sulfonamide potentiators), β-lactams, quinolones, tetracyclines, macrolides, others (streptogramins, lincosamides, phenicols, peptides, aminoglycosides, ansamycins, furanes, and nitroimidazoles), and uncategorized antibiotics (Supplementary Material Table S1) [40].

2.2. Data analysis

The detection status of antibiotics across different continents and environmental compartments globally was visualized using the *ggplot2* package of the R program. For this purpose, Ward's method and asymmetric binary clustering were employed to cluster the presence of antibiotics across eight environmental compartments based on their occurrence. Asymmetric binary clustering was also used to mitigate the impact of different concentration units across various compartments. Based on the clustering results, co-occurrence network diagrams were plotted using Chiplot (https://www.chiplot.online/). Furthermore, to identify representative antibiotics, Euclidean distance matrices, and Ward's clustering method were applied to cluster the antibiotics according to their liquid and solid phases, thereby determining the typical antibiotics. Based on the statistical distribution of the antibiotic data, the concentration values were transformed into base-10 logarithmic concentrations for statistical analysis. The clustering analyses were performed using the *pheatmap* package in R v.4.3.3.

To evaluate the risks posed by antibiotics in the global environment from the perspective of One Health, we developed a probabilistic environmental risk assessment model based on the distribution of antibiotic concentrations in various environmental compartments. The measured environmental concentrations of antibiotics were sorted in ascending order [41], and the percent rank was assigned using a Weibull formula (equation (1)) as follows:

$$j = \frac{100i}{n+1} \quad (1)$$

where j is the percent rank, i refers to the rank of environmental concentration of the antibiotics, and n represents the number of data points. Antibiotic concentrations were plotted using the logarithmic and probability scales in SigmaPlot v.12.0, following which regression lines were fitted to the distribution points. The slope, intercept, and coefficient of determination (R^2) were calculated for each regression related to every environmental compartment and continent. Following this, the slope and intercept were employed to compute the percentile values for each distribution using the following formula (equation (2)) in Microsoft Excel (2016):

$$y = \mathrm{NOR.S.DIST}(m \log_{10}(x) + b) \quad (2)$$

Subsequently, equation (2) was rearranged to calculate the concentration corresponding to the specified centile value, as follows:

$$X = 10^{\left(\frac{\mathrm{NORM.S.INV}(y)-b}{m}\right)} \quad (3)$$

where NORM.S.DIST provides the standard normal cumulative distribution function, x is the threshold, m refers to the regression slope, and b is the intercept. Threshold concentrations were determined at the 1, 5, 25, 50, 75, 95, and 99 percentiles, and the percentage of antibiotics exceeding the thresholds was calculated. Notably, to mitigate the impact of differences in method detection limits across various studies, only the data exhibiting detection concentrations greater than 10 ng L^{-1} or 10 μg kg^{-1} were selected for further analysis. Below these concentration levels, antibiotics were considered undetected.

Drawing on the One Health approach, the antibiotics were assessed using the predicted no-effect concentration for resistance selection ($PNEC_{RS}$) to evaluate the risk of antibiotic resistance development in humans and animals [42]. In the case of environmental health, the minimum inhibitory concentration (MIC) was used to assess the impact of antibiotics on microbial-mediated biogeochemical nitrogen cycling, with the selected MIC values being the lowest concentrations that inhibit these microorganisms, as determined by existing studies [43]. For surface water, groundwater, wastewater from WWTPs, and animal wastewater, we employed the $PNEC_{RS}$ values for the liquid phases, as noted in previous reports [42]. Furthermore, in the absence of $PNEC_{RS}$ values for the solid-phase environmental compartments, the $PNEC_{liquid}$ values were converted into corresponding $PNEC_{solid}$ values using the following formula [44,45]:

$$\mathrm{PNEC}_{solid} = \mathrm{PNEC}_{liquid} \times K_d \quad (4)$$

where K_d represents the solid−water partition coefficient (L kg^{-1}), derived from previous studies on antibiotics [46]. The $PNEC_{RS}$ and K_d values used in this study are listed in Supplementary Material Table S2**,** and the MIC values for the liquid and solid phases are presented in Supplementary Materials Tables S3 and S4, respectively.

3. Results and discussion

3.1. Global distribution patterns of antibiotics

Supplementary Material Figure S1a presents the global pattern of antibiotic distribution based on a set of 22,732 samples comprising 431,441 dataset records. These samples were collected from 46 countries covering five continents: Asia, Europe, the Americas, Africa, and Oceania. Among the countries, China had the highest number of samples and records, totaling 15,598 samples and 229,729 dataset records, which accounted for 68.6% of the overall sample and 53.5% of the total dataset records. A total of 137 antibiotics were analyzed and detected in the global environment (Supplementary Material Fig. S1b). Notably, the number of analyzed and detected antibiotics varied across countries, led by China, the United States, and Spain, with a total of 99, 64, and 39 antibiotics analyzed, and 98, 55, and 38 detected, respectively.

The dataset reviewed in this study encompassed eight environmental compartments—surface water, groundwater, wastewater from WWTPs, animal wastewater, soil, sediment, WWTP sludge, and animal manure (Fig. 1a). Among these, surface water and wastewater from WWTPs accounted for the largest volumes of antibiotics detected in the dataset records, with the dataset for surface water exceeding 10^5 records. Although data sizes for the other compartments were relatively lower, each surpassed 10^3 records. Asia held the largest share of dataset records for each individual compartments, averaging 76% of the total dataset records, followed by the Americas and Europe, which accounted for 14% and 8% of the total dataset records, respectively. The substantial number of dataset records originating from Asia can be attributed to the widespread use of antibiotics in the region. In 2018, Asian countries, such as China, Japan, Singapore, and South Korea, became significant antibiotic exporters to the European Union [47]. Among the Asian countries, the proportion of antibiotic detection was the highest in China, possibly related to the country being the world's largest producer, exporter, and consumer of antibiotics [48]. Moreover, the lack of standardized regulations on antibiotic usage and discharge could also have contributed to higher detections in China [36].

At the continent level, significant disparities were observed in the volume of antibiotic data records, ranging from 8102 records in Oceania to 250,517 in Asia (Fig. 1b). Similar to the results obtained for the distribution of antibiotic data across different environmental compartments, the largest volume of data was also acquired from Asia. In contrast, antibiotics detected from the Africa and Oceania datasets were relatively scarce due to limited existing research data.

Sulfonamides emerged as the most prevalent class of antibiotics across continents, accounting for 44% of the total records in the dataset. Notably, sulfonamides are synthetic antibiotics that are the first clinically successful broad-spectrum antibiotics widely used for both human and veterinary purposes worldwide [49,50]. Subsequently, macrolides ranked second, averaging 24% of the total dataset records. However, in Europe, macrolides comprised the highest proportion, constituting 33% of the dataset records about the region. As protein synthesis inhibitors, macrolides are extensively used in treating human diseases and livestock farming [51]. Despite their relatively short environmental half-life, the continuous input of macrolides into the environment may contribute to their pseudo-persistence, leading to their widespread occurrence in aquatic environments [52,53]. Furthermore, quinolones and tetracyclines exhibited higher proportions in Africa and Asia than in other continents, while comparatively more residue records of β-lactams were found in Europe.

3.2. Co-occurrence of antibiotics in the global environment

To examine the global patterns of antibiotic co-occurrence, which determines the cumulative effects of antibiotics on the environment, we investigated the co-occurrence relationships among different continents about the same type of environmental

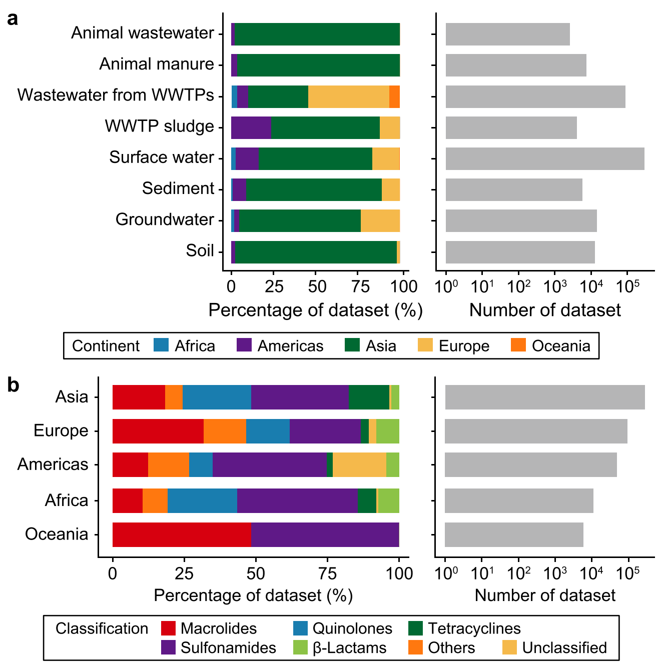

Fig. 1. Antibiotics detected in various continents and environmental compartments worldwide. Wastewater from WWTPs: influents and effluents from wastewater treatment plants; WWTP sludge: sludge from wastewater treatment plants. **a**, Dataset records of various environmental compartments and percentage of dataset records for the five continents concerning each compartment. **b**, Dataset records of various continents and percentage of dataset records with antibiotic classifications for each continent.

compartment, as well as the co-occurrence relationships among various environmental compartments with comparable antibiotic occurrence patterns (Figs. 2 and 3). In the case of liquid compartments (surface water, groundwater, wastewater from WWTPs, and animal wastewater), a total of 125 antibiotics were detected (Fig. 2a). Quinolones and sulfonamides were predominant among the 43 antibiotics that were commonly found in liquid phases across the five continents, showing higher co-occurrence frequency than other pairs of antibiotics (Fig. 2a). β-lactams were found to be most common in Europe, while sulfonamides were predominant in Asia. Concerning the solid phases (soil, sediment, WWTP sludge, and animal manure), 73 antibiotics were detected (Fig. 2b). However, due to the lack of antibiotic data on solid phases in Oceania, only four continents were considered for co-occurrence analysis of the solid phases. Overall, 18 antibiotics were commonly detected across the continents, especially quinolones, tetracyclines, macrolides, and sulfonamides (Fig. 2b). Moreover, a larger number of antibiotics were detected in Asia than in the other continents, possibly due to the widespread use of antibiotics in the region.

The eight environmental compartments were clustered using Ward's method and asymmetric binary to be classified into distinct groups comprising similar antibiotics. Type I included surface water, groundwater, wastewater from WWTPs, and animal wastewater compartments (Supplementary Material Fig. S3). The co-occurrence network of antibiotics that exhibit higher occurrence frequencies in these compartments is presented in Fig. 3a. Type II comprised the soil, sediment, WWTP sludge, animal wastewater, and animal manure compartments (Supplementary Material Fig. S3), the co-occurrence network diagram for which is presented in Fig. 3b. For Type I, 49 of the 126 detected antibiotics appeared in all compartments, while 30 out of 75 antibiotics related to Type II appeared in all compartments (Fig. 3a and b). Notably, sulfonamides and quinolones were commonly present in both types of compartments. Type I contained more β-lactams, reflecting the distribution patterns observed in liquid phases. β-lactams were primarily detected in wastewater from WWTPs and surface water. This observation can be attributed to a β-lactam ring in β-lactams, which makes it prone to hydrolysis or degradation under biotic and abiotic conditions. Since these antibiotics are transformed by environmental migration, a decrease in concentration from the point source to the receptor is usually observed [12,54,55]. As a result, β-lactams were rarely found in the solid phases and Type II compartments.

Sulfonamides emerged as the predominant antibiotics, commonly found across continents and various compartments, primarily due to their solubility in water and comparatively greater resistance to degradation than other antibiotics [56]. Furthermore, in analyzing co-occurrence relationships between continents and environmental compartments, tetracyclines and quinolones stood out as globally essential antibiotics. Notably, tetracyclines are widely used as veterinary drugs, ranking second in the production and consumption of antibiotics worldwide [4], while quinolones, which were detected across various environmental compartments, are antibiotics used in both human and veterinary medicine [57–60]. Due to their high sorption affinity to soil, which lowers their bioavailability, quinolones degrade slowly once they reach anaerobic conditions in groundwater [3]. Meanwhile, lincomycin—a commonly used veterinary antibiotic—was present in both liquid and solid phases across different compartment types, showing high co-occurrence frequency [61], possibly owing to its excessive use and environmental behavior [62]. Lincomycin's high chemical stability and resistance to natural degradation make it relatively persistent in the environment [63,64].

3.3. Concentrations of frequently detected antibiotics in liquid and solid phases

To compare the detection frequencies and concentration of antibiotics in the liquid and solid phases, we sorted the data in descending order based on the number of antibiotics detected to select the top 30 antibiotics for both phases. In the liquid phases, eight antibiotics—sulfamethoxazole, erythromycin, trimethoprim, ciprofloxacin, ofloxacin, norfloxacin, sarafloxacin, and clindamycin—attained detection frequencies exceeding 50% (Fig. 4a), with the frequencies of sulfamethoxazole and trimethoprim surpassing 57% (Fig. 4a). Due to their low cost and proven efficacy against broad-spectrum bacterial infection, these two antibiotics are often used in combination as drugs that are synergistic with sulfonamides [49]. This combination, known as co-trimoxazole, continues to be widely employed in human and veterinary medicine [38,65]. Furthermore, 14 antibiotics were detected more than 10,000 times, with concentrations ranging from 0.25 to 7.08 ng L^{-1} (Fig. 4b; Supplementary Material Table S5). The median concentrations of the different classes of antibiotics were as follows: quinolones (2.47 ng L^{-1}) > tetracyclines (2.05 ng L^{-1}) > macrolides (1.85 ng L^{-1}) > sulfonamides (0.41 ng L^{-1}) (Supplementary Material Table S5). Amoxicillin—the only identified β-lactam antibiotic—had a median concentration of 2.87 ng L^{-1}.

In the solid phases, enrofloxacin and doxycycline, representing quinolones and tetracyclines, respectively, achieved detection frequencies exceeding 50% (Fig. 5a). Notably, these antibiotics appeared more frequently in the solid phases than in the liquid phases, which can be attributed to the ability of quinolones and tetracyclines to form complexes with metal cations, thus greatly enhancing their sorption compared to their respective solid phases [3,66,67]. Overall, nine antibiotics—sulfamethoxazole, norfloxacin, enrofloxacin, ciprofloxacin, sulfamethazine, oxytetracycline, chlortetracycline, sulfadiazine, and tetracycline—were detected more

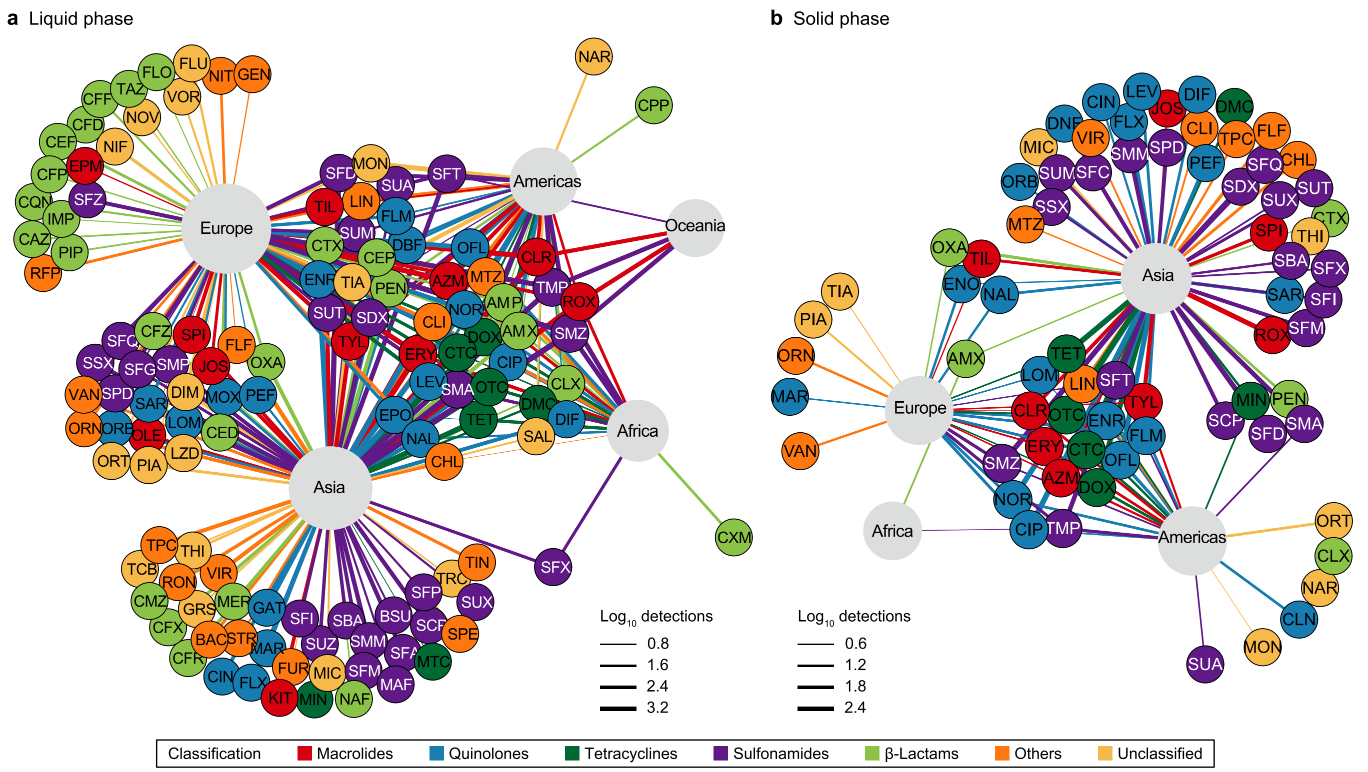

Fig. 2. Co-occurrence relationships of the detected antibiotics across different continents: liquid phase (surface water, groundwater, and wastewater from WWTPs; **a**) and solid phase (soil, sediment, WWTP sludge, animal wastewater, and animal manure; **b**). WWTPs: wastewater treatment plants.

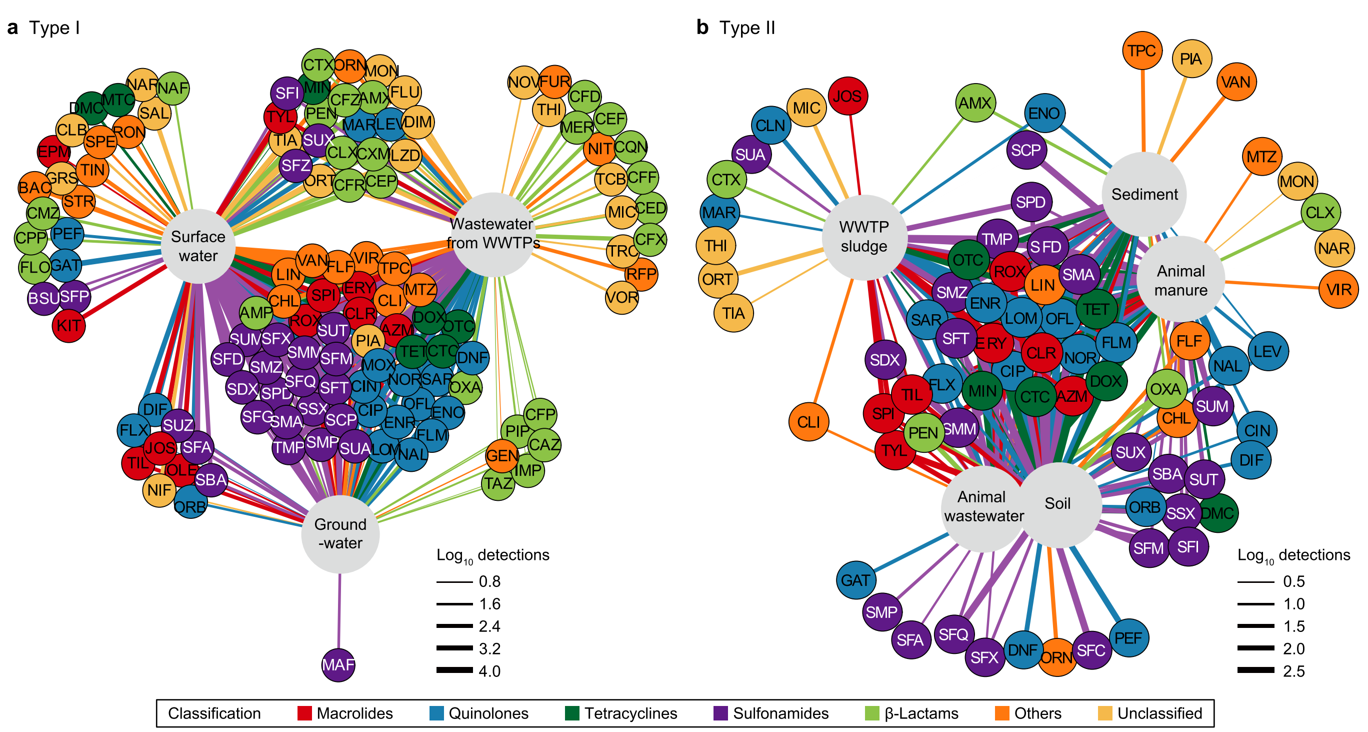

Fig. 3. Co-occurrence of antibiotics in Type I (surface water, wastewater from WWTPs, and groundwater; **a**) and Type II (WWTP sludge, sediment, animal manure, soil, and animal wastewater; **b**) environmental compartments, representing networks with higher and lower occurrence frequencies, respectively. wastewater from WWTPs: influents and effluents from wastewater treatment plants; WWTP sludge: sludge from wastewater treatment plants.

than 1000 times, with concentrations ranging from 0.01 to 0.70 μg kg^{-1}. Among these, lincomycin showed the highest median concentration at 4.15 μg kg^{-1} (Fig. 5b; Supplementary Material Table S6). The median concentrations of the antibiotics belonging to different categories were as follows: sulfonamides (0.27 μg kg^{-1}) > quinolones (0.08 μg kg^{-1}) > tetracyclines (0.04 μg kg^{-1}) > macrolides (0.02 μg kg^{-1}) (Supplementary Material Table S6).

The above analysis highlights that the concentration ranges of individual antibiotics in the solid and liquid phases vary greatly, ranging from ng L^{-1} (or μg kg^{-1}) to mg L^{-1} (or mg kg^{-1}) levels. This points to differences in antibiotic consumption and treatments across various continents and countries, which are possibly linked to the lack of advanced treatment processes or unrestricted use and sale of such products in certain countries [68]. In the liquid phases, sulfonamides exhibited prominent detection frequency, whereas it was significantly reduced in the solid phases. This can be attributed to the fact that the distribution of antibiotics between water and sediment is driven by compound (such as hydrophobicity and functional groups) and sediment properties (such as particle size and composition), resulting in significant variations in the sediment−water partition coefficients of antibiotics [69,70]. The high adsorption levels of quinolones and tetracyclines primarily stem from their strong polarity and multiple ionic groups [71,72]. In contrast, macrolides have fewer functional groups, resulting in lower adsorption [73]. Meanwhile, sulfonamides, which contain only aniline and amide groups, demonstrate weaker adsorption capabilities in soil [74]. Overall, macrolides, quinolones, and trimethoprim are more prone to sedimentation in their solid phases than sulfonamides and tetracyclines [68].

3.4. Classification and prioritization of antibiotics with high detection frequencies and concentrations

Fig. 6 depicts the hierarchical clustering analysis employed to classify and prioritize antibiotics in the liquid and solid phases [38]. The classification aimed to identify antibiotics exhibiting high detection concentrations across various compartments on different continents, indicating high detection frequency. In the case of the liquid phases, the antibiotics were grouped into Clusters I and II, representing different concentration ranges. Cluster I comprised 15 antibiotics with low detection frequencies (average frequency less than 40%) and low concentrations (average concentration less than 0.005 ng L^{-1}). Within Cluster II, Subgroup IIa consisted of five antibiotics with medium detection frequencies (average frequency is 40−50%) and medium concentrations (average concentration less than 0.05 ng L^{-1}), while Subgroups IIb and IIc comprised ten antibiotics (sulfamethoxazole, trimethoprim, ofloxacin, azithromycin, erythromycin, sulfamethazine, ciprofloxacin, norfloxacin, clarithromycin, and roxithromycin) with high detection frequencies (average frequency more than 50%) and high concentrations (average concentration more than 0.05 ng L^{-1}), involving sulfonamides, quinolones, and macrolides classes of antibiotics (Fig. 6a). Notably, Subgroups IIb and IIc were the dominant contaminants in the liquid phases. Furthermore, antibiotics with similar uses or chemical structures tended to cluster into specific subgroups. For instance, Subgroup IIa primarily consisted of tetracyclines, Subgroup IIb included synergistic sulfonamide combinations, while Subgroup IIc mainly comprised quinolones and macrolides. Notably, clustering antibiotics into these subgroups aligns with common usage patterns and environmental behaviors globally [75,76].

Regarding geography, antibiotics were mainly found to be distributed across Clusters I and II in the case of Asia and Europe, exhibiting relatively low detection concentrations. In the Americas, higher concentrations, particularly of sulfonamides, were found concerning Subgroup Ia and Cluster II, with wastewater from WWTPs exhibiting an increased concentration (25.88 ng L^{-1}) compared to the other environmental compartments. In this context, Karthikeyan and Meyer [77] examined seven Wisconsin-based wastewater treatment plants to detect trimethoprim in 80% of the influent and effluent samples, while sulfamethoxazole was found in 70% of the samples. Furthermore, in the case of Africa, Cluster II showed elevated antibiotic concentrations, with surface water exhibiting the highest concentrations (58.58 ng L^{-1}) among all compartments. This region is not discussed here due to limited and potentially unrepresentative data from Oceania. In general, despite regional differences in antibiotic detection concentrations, it was observed that the overall distribution of the antibiotics found in high concentrations follows similar patterns.

As for the solid phases, antibiotics were classified into Clusters III and IV, representing different concentration patterns. Cluster III comprised 11 antibiotics that exhibited low detection frequencies (average frequency less than 40%) and low concentrations (average concentration less than 0.005 μg kg^{-1}). Meanwhile, in Cluster IV, Subgroups IVa and IVd consisted of 11 antibiotics with low detection frequencies (less than 40%) and medium concentrations (average concentration less than 0.05 μg kg^{-1}), while Subgroups IVb and IVc comprised eight antibiotics featuring medium detection frequencies (average frequency is 40−50%) and high concentrations (average concentration more than 0.05 μg kg^{-1}), including three tetracyclines (chlortetracycline, doxycycline, and tetracycline) and five quinolones (ciprofloxacin, norfloxacin, enrofloxacin, lomefloxacin, and ofloxacin) (Fig. 6b). In this context, it must be noted that previous studies have reported high residual concentrations of norfloxacin, ofloxacin, and ciprofloxacin in various environmental samples worldwide [78−80].

Regarding regional distribution, Clusters III and IV antibiotics were detected in Asia, but their concentrations were relatively low. In Europe, higher detection frequencies were observed for Cluster IV, particularly for quinolones in Subgroup IVc. Meanwhile, higher antibiotic concentrations were observed in the Americas for Cluster IV, particularly in sediments and WWTP sludge, which showed average concentrations of 42.90 and 20.33 μg kg^{-1}, respectively. The detection frequencies and concentrations of quinolones were considerably high in both the Americas and Europe [81]. As one of the most widely used antibiotics in veterinary medicine, quinolone use in food-producing animals in the United States increased by 26% from 2016 to 2018 [82,83]. Notably, due to limited data on antibiotics in solid phases from Africa, no analysis could be conducted for this region.

The priority antibiotics identified through the cluster analysis conducted in this study were similar to those identified by Huang et al. [38] in their study on various environmental compartments in China. Specifically, both studies identified oxytetracycline, sulfamethoxazole, sulfamethazine, ofloxacin, ciprofloxacin, and norfloxacin as high-detection and high-concentration antibiotics in the liquid phases. Similarly, in the case of the solid phases, high concentrations of tetracycline, chlortetracycline, ofloxacin, enrofloxacin, norfloxacin, and ciprofloxacin were identified. These findings point to significant similarities in antibiotic usage patterns and environmental exposure between the global and Chinese contexts, further suggesting that antibiotic pollution may proliferate through transboundary water flow [49].

3.5. Risk assessment from the One Health perspective

Driven by a One Health perspective, risk assessments conducted in this study focused on the impact of antibiotics on human, animal, and ecological health. We employed $PNEC_{RS}$ and MIC to assess the

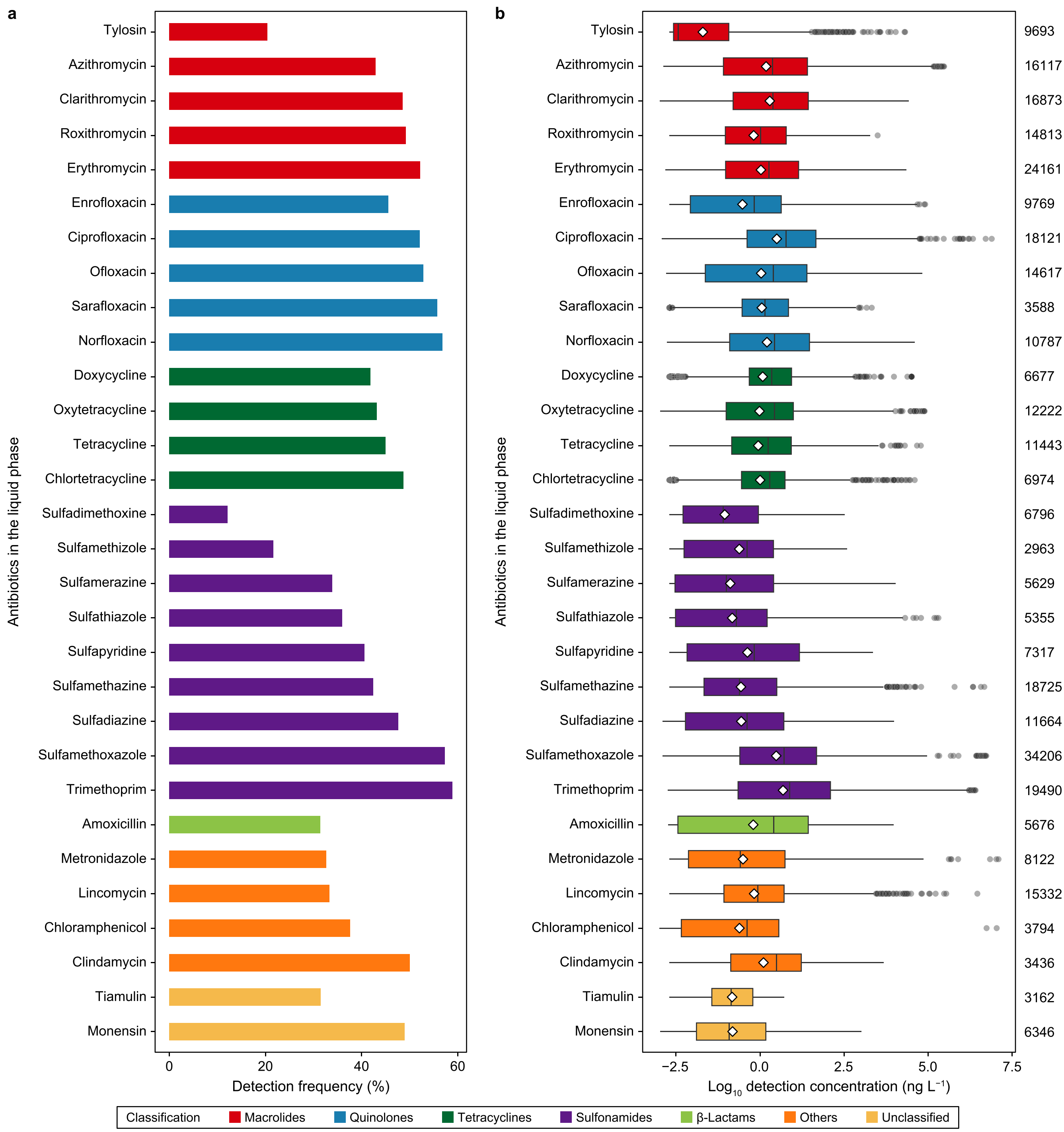

Fig. 4. Detection frequency (**a**) and $\log_{10}$ transformed concentrations (**b**) of antibiotics in liquid phases on a global scale. The numbers on the right indicate the amounts of each detected antibiotic.

risks associated with antibiotic resistance and ARGs and their effects on microorganisms involved in the nitrogen cycle. Probabilistic environmental risk assessment revealed the predicted threshold concentrations corresponding to different percentiles of environmental exposure levels derived from the measured antibiotic concentrations (Supplementary Material Table S7–S9).

3.5.1. Risk assessment of antibiotics in the liquid phases

Antibiotics whose detection frequencies exceeded 40% and comprised at least 11 sampling points were selected for risk assessments (except amoxicillin, 31%). When using $PNEC_{RS}$ as the threshold, ciprofloxacin was identified as the antibiotic posing the highest risk, exceeding the $PNEC_{RS}$ threshold for wastewater from WWTPs, surface water, and groundwater by 62%, 36%, and 12%, respectively (Fig. 7; Supplementary Materials Fig. S4 and Table S7).

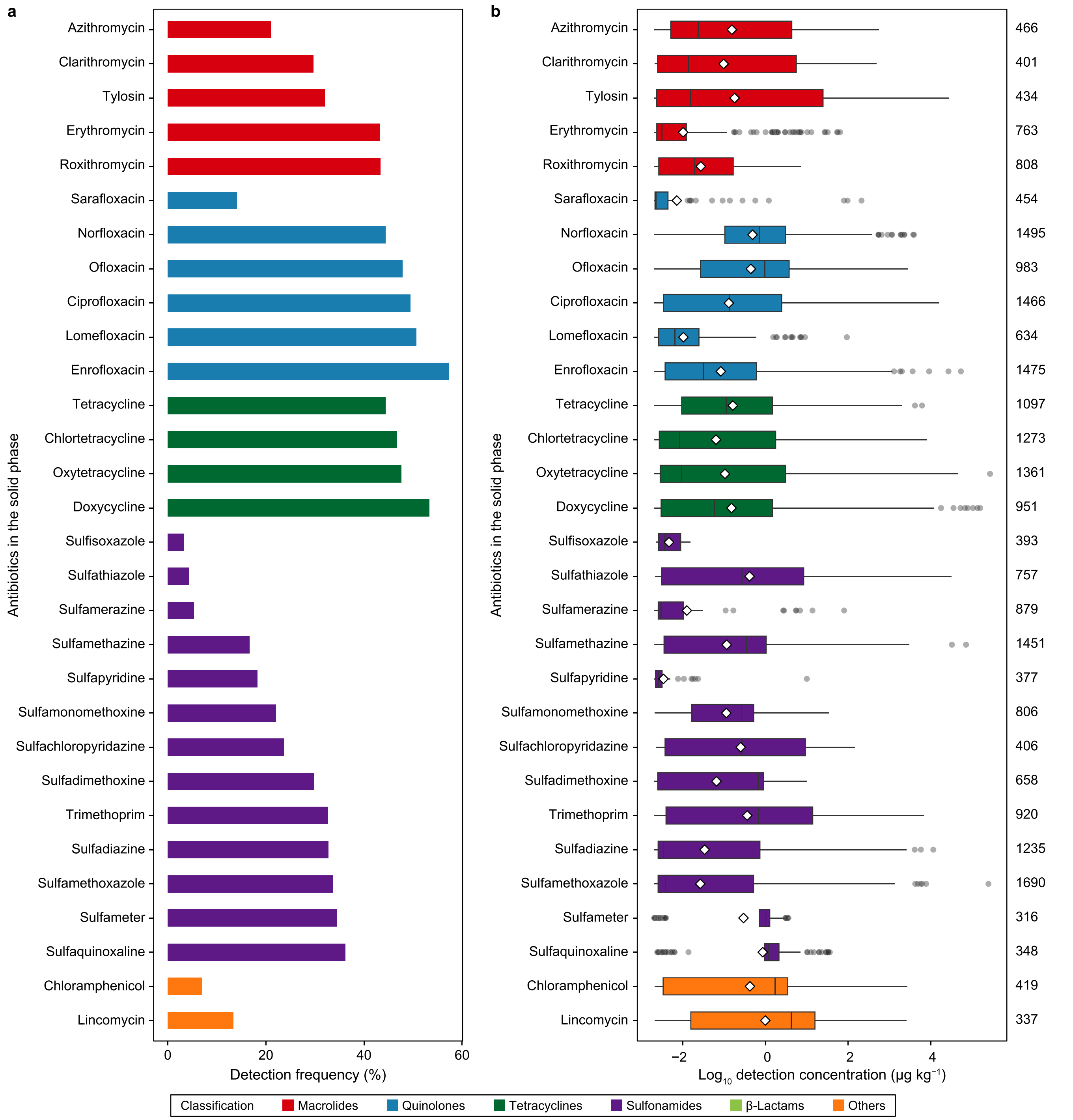

Fig. 5. Detection frequency (**a**) and $\log_{10}$ transformed concentrations (**b**) of antibiotics in solid phases on a global scale. The numbers on the right indicate the amount of each detected antibiotic.

Wastewater from WWTPs emerged as the environmental compartment of highest concern, with over 21% of its samples containing antibiotic concentrations that exceeded the threshold. Furthermore, based on their probability of exceeding the threshold, the liquid environmental compartments were ranked as follows: wastewater from WWTPs > surface water > animal wastewater > groundwater (Fig. 7). This finding is consistent with those of [41], who conducted a risk assessment of antibiotics found in liquid phases across the Western Pacific and Southeast Asia. Overall, this finding indicates the existence of common sources and pathways of antibiotic pollution across different global regions.

When using MIC as the threshold, both ciprofloxacin and ofloxacin were found to be high-risk antibiotics. Ciprofloxacin exceeded the MIC threshold by 52% in the case of wastewater from WWTPs and by 9% for both surface water and groundwater. Meanwhile, ofloxacin exceeded the MIC threshold for wastewater

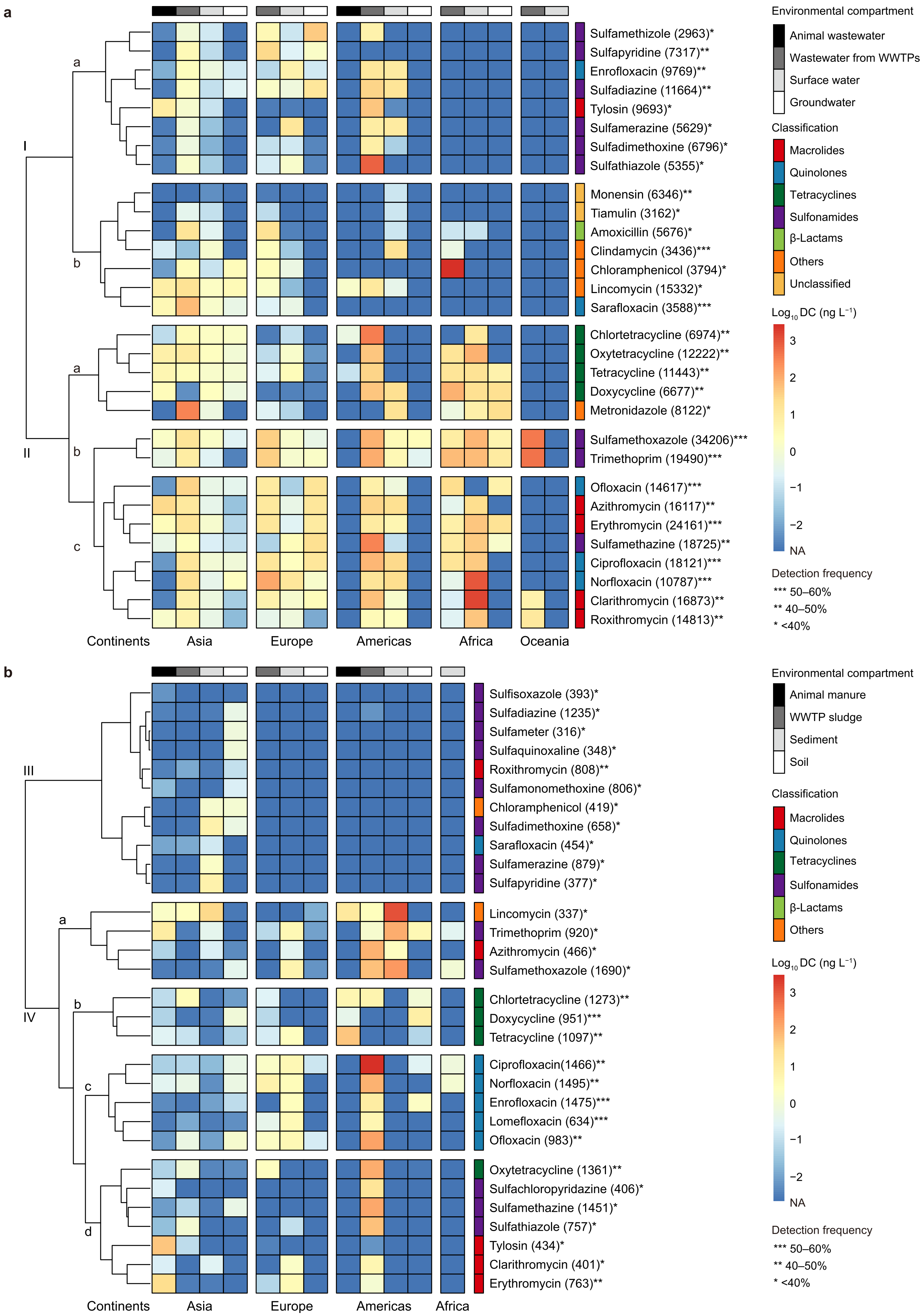

Fig. 6. Heatmap illustrating the clustering of logarithmic concentration values of the top 30 antibiotics in the liquid phases (**a**) and solid phases (**b**). Log_{10} DC: Log_{10} detected concentration.

from WWTPs by 52%, while the exceedance percentages for surface water and groundwater were 15% and 4%, respectively (Fig. 7; Supplementary Material Table S7). Overall, wastewater from WWTPs was identified as the environmental compartment posing the highest risk, achieving an average exceedance percentage of 19%. Among the antibiotics, trimethoprim, ciprofloxacin, and ofloxacin exceeded the MIC threshold by over 20% (Fig. 7; Supplementary Material Table S7).

Previous studies have shown that WWTPs act as the ultimate receptor of antibiotics in urban areas, with effluents being one of the primary anthropogenic sources of antibiotics [38,84]. Based on the $PNEC_{RS}$ and MIC calculations, wastewater from WWTPs was found to carry the highest risk. This indicates that, at present, WWTPs do not completely remove antibiotics and that various antibiotics exhibit significant differences in removal efficiency. In other words, WWTPs serve as major reservoirs of antibiotic residues and resistance, with their effluents considered one of the main sources of ARGs [85,86]. Notably, metagenomic analysis has revealed that the interactions of ARBs, ARGs, and mobile genetic elements in WWTPs can facilitate the transfer of resistance genes among different bacterial species, thus posing risks to animal and human health [87,88]. Additionally, high concentrations of residual antibiotics can inhibit the activity of nitrifying microorganisms, leading to increased emissions of nitrous oxide, a greenhouse gas [20,89]. Although the risk presented by antibiotics to nitrogen-cycling microorganisms is generally lower compared to the potential harm from ARG generation, the environmental impacts of antibiotics are quite significant and should not be overlooked [18].

3.5.2. Risk assessment of antibiotics across different continents

After assessing the probability of environmental hazards caused by the antibiotics in various liquid phases, we selected the antibiotics whose concentrations indicated a high probability of exceeding the $PNEC_{RS}$ ($\geq$21.82%) for risk assessment across different continents (Fig. 8; Supplementary Materials Fig. S5 and Table S8). According to the analysis results, the concentrations of all selected antibiotics showed the highest probability of exceeding the $PNEC_{RS}$ and MIC thresholds in the case of Africa, with an average exceedance probability of 53%, followed by the Americas (38%), Europe (27%), and Asia (24%) (Supplementary Material Table S8). Among the antibiotics, the highest exceedance proportion in Africa was observed for ciprofloxacin in wastewater from WWTPs, which reached 65% (Fig. 8; Supplementary Material Table S8). Africa's high-risk condition can be attributed to the extensive misuse of antibiotics, lack of wastewater treatment facilities, and direct discharge of most wastewater into surface waters in the continent [90,91]. For instance, statistics drawn from 13 to 27 African countries revealed that 3558–4279 tons of antimicrobial drugs were used between 2015 and 2019 solely for animals [92]. In addition, although overall antibiotic usage in Asia was substantial, the average exceedance proportion of the selected antibiotics was not as high as in the other continents (Fig. 8).

When using $PNEC_{RS}$ as the threshold, ciprofloxacin emerged as the antibiotic, presenting the highest risk across all continents, with the highest exceedance proportion of 66% observed for Europe. Similarly, when using MIC as the threshold, ciprofloxacin was the highest-risk antibiotic in Europe and the Americas, with 56% and 55% of the measured concentrations exceeding the threshold, respectively. In contrast, ofloxacin was the highest-risk antibiotic in Africa and Asia, with 63% and 46% of the measured concentrations exceeding the MIC threshold, respectively (Fig. 8; Supplementary Material Table S8). Notably, conventional water treatment methods cannot remove ciprofloxacin effectively, and it cannot be degraded by abiotic processes in aquatic ecosystems, thereby facilitating its widespread distribution across continents and the emergence of resistance genes [93–96]. Meanwhile, ofloxacin exhibits a higher toxic effect on the *amoA* gene of ammonia-oxidizing bacteria (AOB) than on that of ammonia-oxidizing archaea (AOA) during the nitrification process, potentially leading to functional redundancy between the *amoA*-AOA and *amoA*-AOB communities [97].

3.5.3. Risk assessment of antibiotics in the solid phases

We selected antibiotics exhibiting detection frequencies greater than 40% corresponding to more than seven sampling points to assess the risk posed by antibiotics in the solid environmental compartments. The selected antibiotics were enrofloxacin, norfloxacin, ofloxacin, oxytetracycline, and doxycycline, which belong to the quinolone and tetracycline classes (Fig. 9; Supplementary Material Fig. S6). The analysis using $PNEC_{RS}$ as the threshold revealed enrofloxacin to be the antibiotic presenting the highest risk, achieving a maximum exceedance ratio of 96% and a minimum of 47%. Notably, enrofloxacin cannot be easily degraded by environmental microorganisms, and its carboxyl group reacts with the organic matter in manure to form complexes or chelates [98]. Meanwhile, oxytetracycline displayed a maximum exceedance percentage of 64%. Animal manure was identified as the environmental compartment posing the highest risk, with its average proportions exceeding the $PNEC_{RS}$ threshold to reach 68%.

When using MIC as the threshold, norfloxacin exhibited the highest probabilistic risk. In particular, 24% and 21% of the animal manure and sediment samples had norfloxacin concentrations exceeding the MIC threshold (Supplementary Material Table S9). Norfloxacin can inhibit nitrate reductase activity in the denitrification process and, to some extent, enhance nitrite reductase activity, leading to increased nitrous oxide emissions [99]. Furthermore, similar to the observations made using $PNEC_{RS}$ as the threshold, animal manure was identified as the environmental compartment with the highest risk when considering MIC (Supplementary Material Table S9). The average proportion of animal manure samples exceeding the MIC threshold was 20%—higher than that for other solid environmental compartments (Fig. 9; Supplementary Materials Fig. S6 and Table S9). Risk ranking for the different environmental compartments was as follows: animal manure > sediment > WWTP sludge > soil. Since animals cannot fully absorb metabolized antibiotics, they excrete them through feces and urine, leading to a high proportion of antibiotics in animal manure that exceed threshold concentrations [100]. Furthermore, people may directly deposit animal feces on the ground or use them as fertilizer on soil, resulting in increased antibiotic concentrations in other environmental compartments and contributing to the proliferation of ARGs, along with heavy metals such as Cu and Zn [101,102]. Overall, the proportion of antibiotics exceeding the MIC threshold concentration was lower than that exceeding the $PNEC_{RS}$ threshold, indicating a higher probability of antibiotic resistance risk. Notably, further analysis at the continent level could not be conducted due to limited data points available for the solid compartments.

3.6. Data gaps and prospects for antibiotic assessment from a One Health perspective

This study has several limitations. First, data imbalance is a significant concern. The limited amount of research data available for several countries and specific environmental compartments, such as solid phase data for Africa and data about Oceania as a whole, may compromise the comprehensiveness and representativeness of our findings. Second, while risk assessments were conducted based on $PNEC_{RS}$, this method is characterized by inherent uncertainties, including variations in data sources, gene

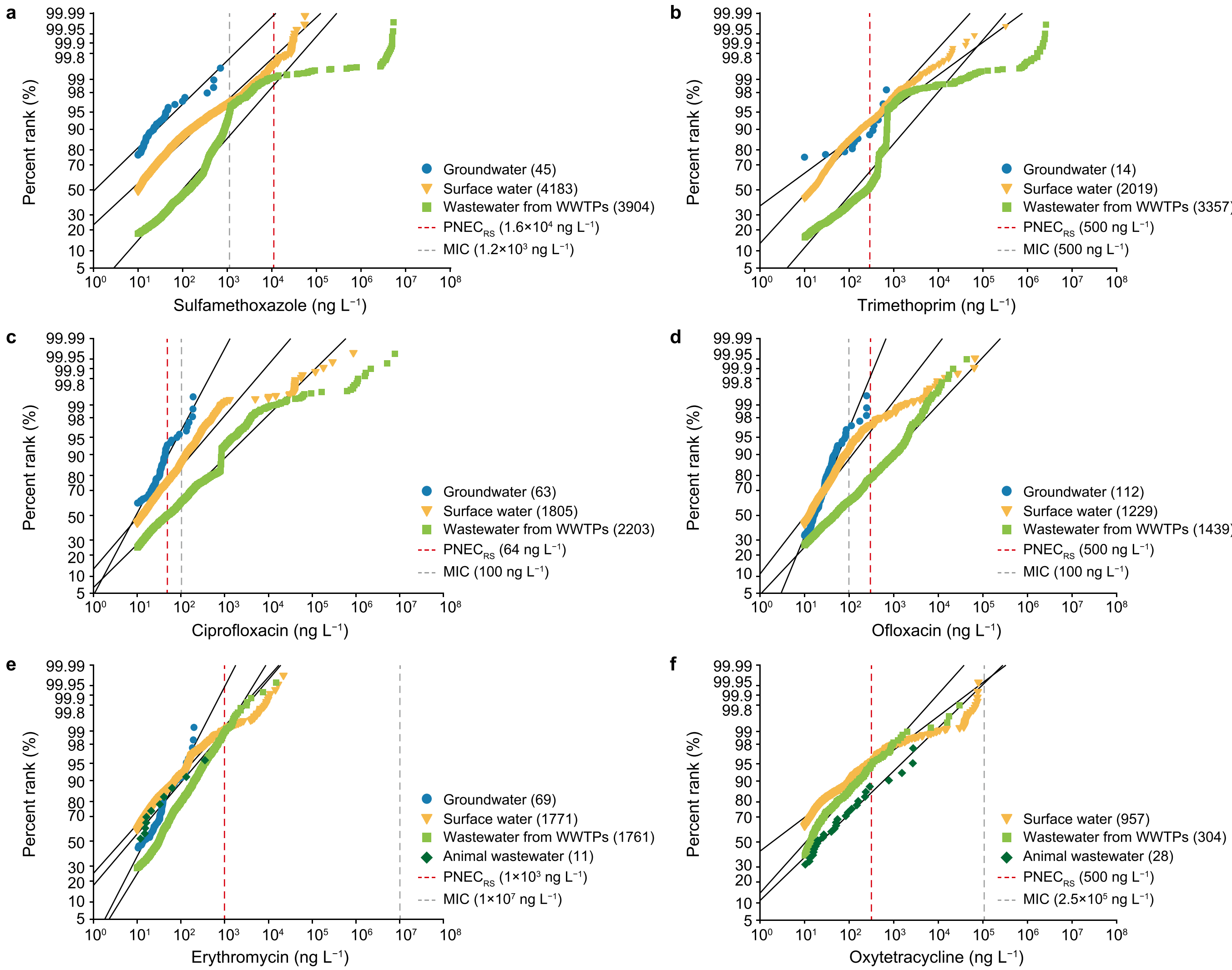

Fig. 7. Environmental exposure distribution of antibiotic concentrations detected in liquid environmental compartments across the globe: **a**, sulfamethoxazole; **b**, trimethoprim; **c**, ciprofloxacin; **d**, ofloxacin; **e**, erythromycin; **f**, oxytetracycline. The vertical lines correspond to the predicted no-effect concentration for antibiotic resistance (PNEC$_{RS}$) and the minimum inhibitory concentration (MIC). The numbers in parentheses represent the number of data points or values corresponding to PNEC$_{RS}$ (ng L^{-1}) and MIC (ng L^{-1}).

transmission complexity, experimental conditions, microbial diversity, long-term effects, and indirect health impacts [41]. These factors may result in either the overestimation or underestimation of risks. Third, there is a lack of research on the inhibitory effects of some antibiotics, such as sulfonamides, on microorganisms involved in the nitrogen cycle. Fourth, although MIC values used in this study were drawn from existing experiments, they could still affect risk assessment accuracy. Furthermore, discrepancies in PNEC$_{RS}$ and MIC data availability—some environmental compartments may have either PNEC$_{RS}$ or MIC values—can result in incomplete or inconsistent assessments. Therefore, future research should comprehensively account for all these factors to improve the accuracy and reliability of risk assessments, thereby providing scientific evidence for developing more effective environmental management strategies. Fifth, the lack of a standardized antibiotic detection methodology and variations in laboratory conditions and preprocessing methods is a barrier to data normalization and comparability. Although we ensured the selection of the same antibiotic detection methods in this study—over 88% of the referenced studies employed tandem mass spectrometry—issues about data normalization and standardization continue to exist. Therefore, a unified and standardized antibiotic detection methodology must be urgently established to ensure data consistency and comparability, enhancing related research's scientific rigor and effectiveness.

The current limitations of this study highlight the need for novel strategies to mitigate antibiotic pollution. This study's findings indicate that Asia, featuring high antibiotic detection frequencies, and Africa, which exhibited high risk of antibiotic resistance, require stronger antibiotic monitoring. Specifically, the control of antibiotics such as ciprofloxacin and ofloxacin in liquid phases and enrofloxacin and norfloxacin in solid phases should be prioritized. Additionally, the high risks associated with environmental media, such as wastewater from WWTPs and animal manure, call for further research into wastewater discharge, treatment processes, and antibiotic regulation. Challenges such as weak infrastructure, low education, low gross domestic product (GDP) per capita, and limited healthcare spending in low- and middle-income countries have resulted in critical antibiotic monitoring and research gaps [103]. Future studies should focus on in-depth research into

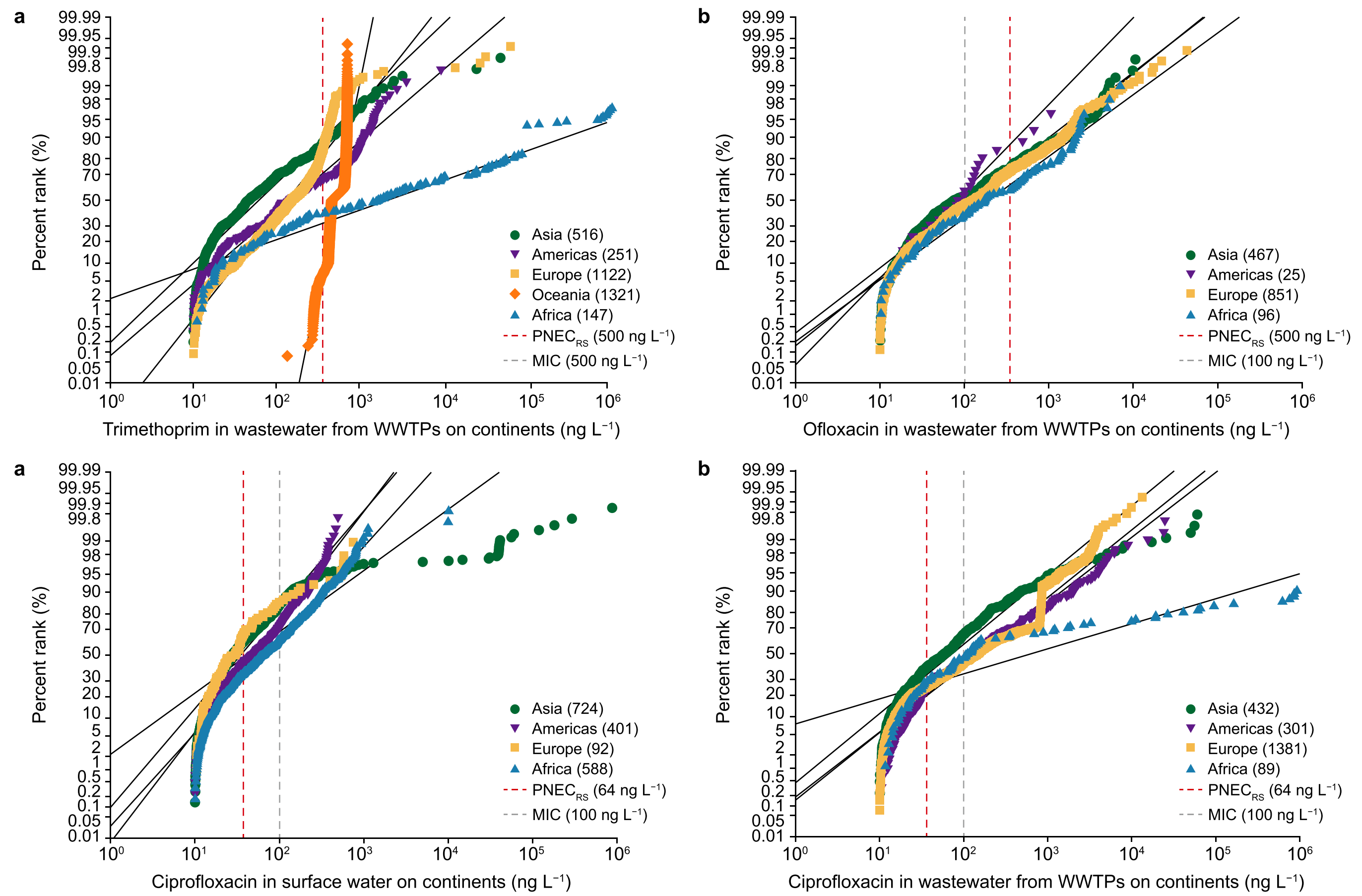

Fig. 8. Environmental exposure distribution of antibiotic concentrations detected in the liquid environmental compartment across continents: **a**, trimethoprim in wastewater from WWTPs; **b**, ofloxacin in wastewater from WWTPs; **c**, ciprofloxacin in surface water; **d**, ciprofloxacin in wastewater from WWTPs. The vertical lines correspond to the predicted no-effect concentration for antibiotic resistance ($PNEC_{RS}$) and the minimum inhibitory concentration (MIC). The numbers in parentheses represent the number of data points or values corresponding to $PNEC_{RS}$ (ng L^{-1}) and MIC (ng L^{-1}).

antibiotics and ARGs in these regions to address these. Furthermore, to tackle the ecological risks that antibiotics pose, their use in humans and animals must be reduced. This necessitates a One Health approach, which promotes global multidisciplinary coordination. Establishing emission standards based on One Health principles will support sustainable public health and environmental protection [41].

4. Conclusion

Based on the perspective of One Health, this study analyzed 253 research articles on the global distribution of antibiotics to identify a total of 137 antibiotics. The analysis results indicate significant variations in antibiotic detection across countries and regions. Overall, sulfonamides emerged as the most widely distributed antibiotic across all continents, followed by macrolides. Furthermore, quinolones and tetracyclines were more prevalent in Asia and Africa, while β-lactams were more common in Europe. Concerning the various environmental compartments considered in this study, sulfonamides exhibited the highest detection frequency in the liquid phases, with median concentrations of the different antibiotic classes being quinolones (2.47 ng L^{-1}) > tetracyclines (2.05 ng L^{-1}) > macrolides (1.85 ng L^{-1}) > sulfonamides (0.41 ng L^{-1}). In the case of solid compartments, quinolones, and tetracyclines showed the highest adsorption levels, with median concentrations of the different antibiotic classes being sulfonamides (0.27 μg kg^{-1}) > quinolones (0.08 μg kg^{-1}) > tetracyclines (0.04 μg kg^{-1}) > macrolides (0.02 μg kg^{-1}). Furthermore, through hierarchical clustering, ten priority antibiotics were identified in the liquid and eight in the solid phases. In the Americas, antibiotic concentrations were highest in WWTP for both solid and liquid phases, while surface water accounted for the highest concentration of antibiotics in Africa. Meanwhile, in Asia and Europe, antibiotic concentrations were relatively lower across all environmental compartments. In addition, risk assessment of the priority antibiotics in liquid and solid phases revealed that wastewater from WWTPs and animal manure pose the highest risks, with 21% and 68% of their samples exceeding the $PNEC_{RS}$ threshold and 19% and 20% exceeding the MIC threshold, respectively. Africa exhibited the highest overall risk about the assessed antibiotics—trimethoprim, ofloxacin, and ciprofloxacin—with an average exceedance percentage of 53%. Furthermore, ciprofloxacin and ofloxacin were identified as the antibiotics posing the highest risk in the liquid phases, while enrofloxacin and norfloxacin presented the most risk in the solid phases.

This study contributes to optimizing the use and prescription practices of human and veterinary antibiotics by providing a foundation for identifying effective measures to prevent and control antibiotic misuse. It also emphasizes the need for further targeted, comprehensive, and in-depth investigations into antibiotic pollution. Such efforts are crucial for acquiring a better

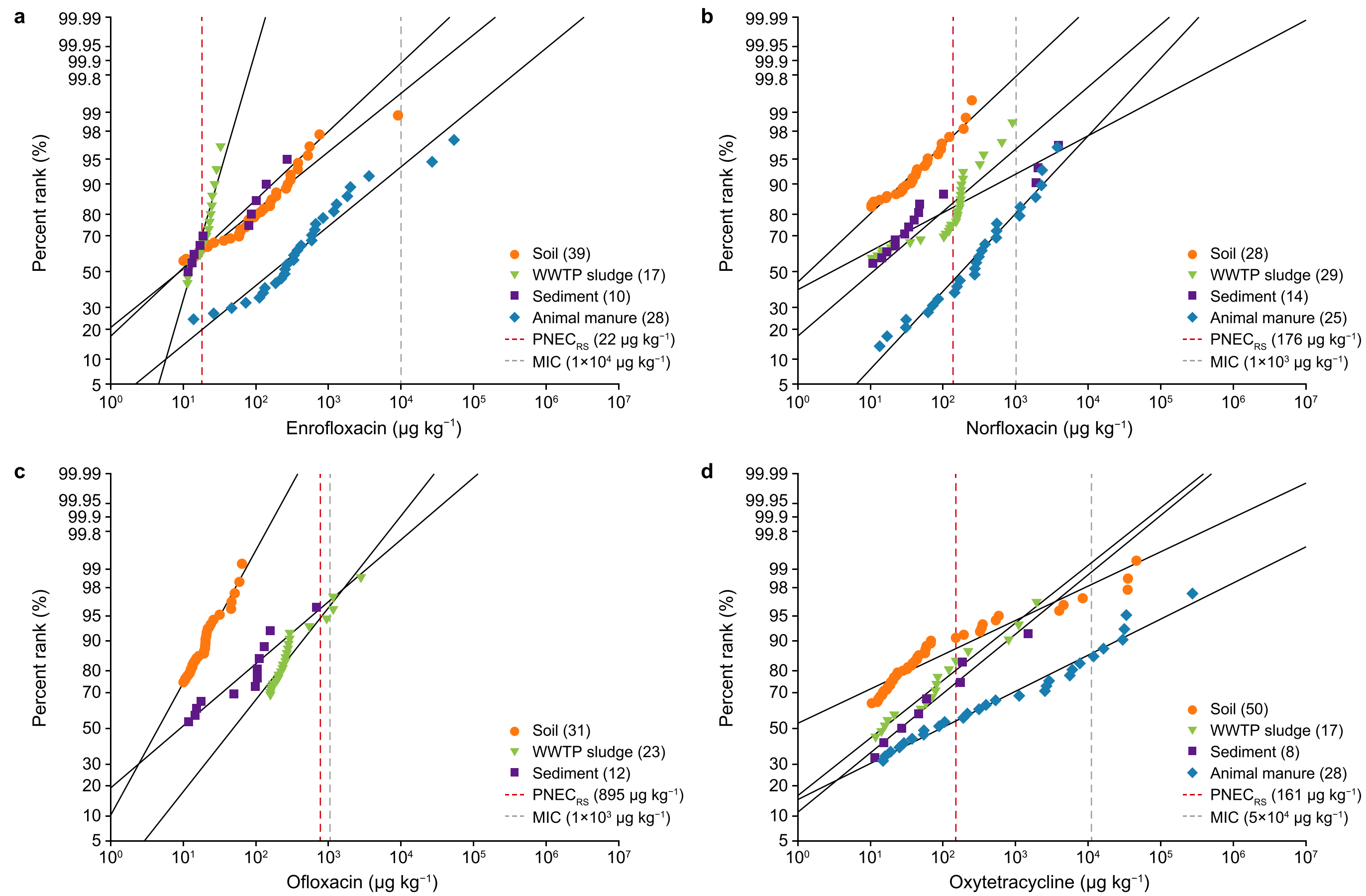

Fig. 9. Environmental exposure distribution of antibiotic concentrations detected in solid environmental compartments across the globe: **a**, enrofloxacin; **b**, norfloxacin; **c**, ofloxacin; **d**, oxytetracycline. The vertical lines correspond to the predicted no-effect concentration for antibiotic resistance ($PNEC_{RS}$) and the minimum inhibitory concentration (MIC). The numbers in parentheses represent the number of data points or values corresponding to $PNEC_{RS}$ (ng L^{-1}) and MIC (ng L^{-1}).

understanding of the global distribution of antibiotics and addressing the health threats faced by humans, animals, and the environment.

CRediT authorship contribution statement

Bingshuang Yan: Writing - Original Draft, Visualization, Formal Analysis, Investigation, Methodology. **Fuyang Huang:** Writing - Review & Editing, Software, Funding Acquisition, Conceptualization, Visualization. **Jiaolong Ying:** Investigation, Software, Validation. **Dafang Zhou:** Data curation, Investigation. **Samira Norouzi:** Writing - Review & Editing, Validation. **Xianming Zhang:** Writing - Review & Editing, Methodology, Conceptualization. **Bin Wang:** Writing - Review & Editing, Supervision. **Fei Liu:** Supervision, Conceptualization.

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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Appendix A. Supplementary data

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