# The occurrence and distribution of antibiotics in the Karst river system in Kaiyang, Southwest China

Shengzhang Zou, Fuyang Huang, Liang Chen and Fei Liu

## ABSTRACT

To our knowledge, this was the first study to investigate the occurrence and distribution of antibiotics in the Karst river system in Kaiyang, Southwest China. Ten water samples were collected from the Karst river in Kaiyang, Southwest China. Thirty-five antibiotics, including nine sulfonamides, four tetracyclines, five macrolides, sixteen quinolones and chloramphenicol, were analyzed. The results suggest that antibiotics are widely prevalent in the Karst river, with macrolides and quinolones being the most dominant and occupying 47% and 43% of total antibiotic concentration, respectively. The maximum total concentrations of sulfonamides, tetracyclines, macrolides, and quinolones were 30.4, 421, 884, and 1,807 ng/L, respectively. Lincomycin, roxithromycin, nalidixic acid, ofloxacin, and norfloxacin were detected in all samples with a detection frequency of 100%. The main sources of antibiotics were wastewater treatment plants (WWTPs) and rural dumps that did not contain sanitary treatment, which accounted for 33% and 40% of the total antibiotics present in the Karst river. Due to an increase in river flow quantity, the presence of WWTPs and rural dumps did not affect the concentration and distribution of antibiotics in the Karst river; however, the mass flux of antibiotics were significantly affected by the contamination source and the poor natural attenuation.

**Key words** | antibiotics, distribution, Karst, river, occurrence

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## INTRODUCTION

Antibiotics are widely used to prevent and treat diseases pertaining to humans and livestock. Due to their lower adsorption rates, the majority of antibiotics can enter into the environment in the form of unchanged compounds and their metabolites (Sarmah *et al.* 2006). As a result, they have been detected in different environments including wastewater treatment plants (WWTPs) (Wu *et al.* 2016; Subedi *et al.* 2017), landfill (Song *et al.* 2016), surface water (Paiga *et al.* 2016; Xu *et al.* 2016), sediment (Dong *et al.* 2016), soil (Gao *et al.* 2015), groundwater (Balzer *et al.* 2016; Yao *et al.* 2017), and drinking water (Simazaki *et al.* 2015). Bai *et al.* (2014) reported that the concentrations of erythromycin-$H_2O$ and sulfamethoxazole (SMX) in water of the Liao River Basin are 2,834 and 1,484 ng/L, and the total concentration of antibiotics in Taihu Lake is 2,700 ng/L (Zhou *et al.* 2016). The highest concentration of SMX (765 ng/L) and erythromycin (ERY, 25 μg/kg) in water and sediment of the Huangpu River were also observed by Chen & Zhou (2014).

Karst river and its corresponding aquifers are an important source for drinking water in the Karst area, especially in southwestern China (Ford & Williams 2007; Jiang & Yan 2010). However, Karst aquifers are easily contaminated due to the unique hydrogeological characteristics of high hydraulic conductivity and short residence time (Hillebrand *et al.* 2015). In recent years, organic pollutants have been frequently detected in the Karst area. Alam *et al.* (2014) found that the concentration of organochlorine pesticides in the Nanshan underground river system ranged from 61 to 936 ng/L in groundwater and from 51 to 3,842 ng/g in sediment. Antibiotics such as SMX (72.9 ng/L), trimethoprim

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(15.5 ng/L), and ofloxacin (OFL, 4.2 ng/L) were also detected in the Karst river in Eastern France (Chiffre *et al.* 2016).

In this study, the occurrence and distribution of antibiotics in the Karst river system in Kaiyang, Southwest China, was investigated. Ten sampling sites were selected and 35 antibiotics including nine sulfonamides, four tetracyclines, five macrolides, sixteen quinolones and chloramphenicol were quantified by using solid phase extraction (SPE) combined with ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS).

## EXPERIMENTAL DESIGN

### Study area and sampling

The study area (59 $km^2$) was located in Kaiyang, Southwest China. Two Karst river systems (the North and South river) were selected, including four underground river entrances (K3, K4, K8 and K9) and three underground river outlets (K5, K8, K10; Figure 1). There were no large-scale livestock farms in the study area; however, a WWTP and rural household garbage dump were located near the South river. The WWTP effluent and dump sewage were directly discharged into the river. The domestic sewage of Shitou village was also discharged into the North river and a drinking water source of the surrounding rural residents was located near K7, which was the outlet of another underground river system without hydraulic connections with other outlets and entrances.

The average width of the survey river is <10 m and the average depth of the water is <1 m. Aqueous samples were collected by the Institute of Karst Geology, Chinese Academy of Geological Sciences and China University of Geosciences (Beijing) (CUGB) following standard sampling procedures (China Geological Survey 2008; Yan *et al.* 2013; Xu *et al.* 2016; Chen *et al.* 2017). All samples were collected from the middle of the flowing water in the middle width of the river in December (dry season). After sample

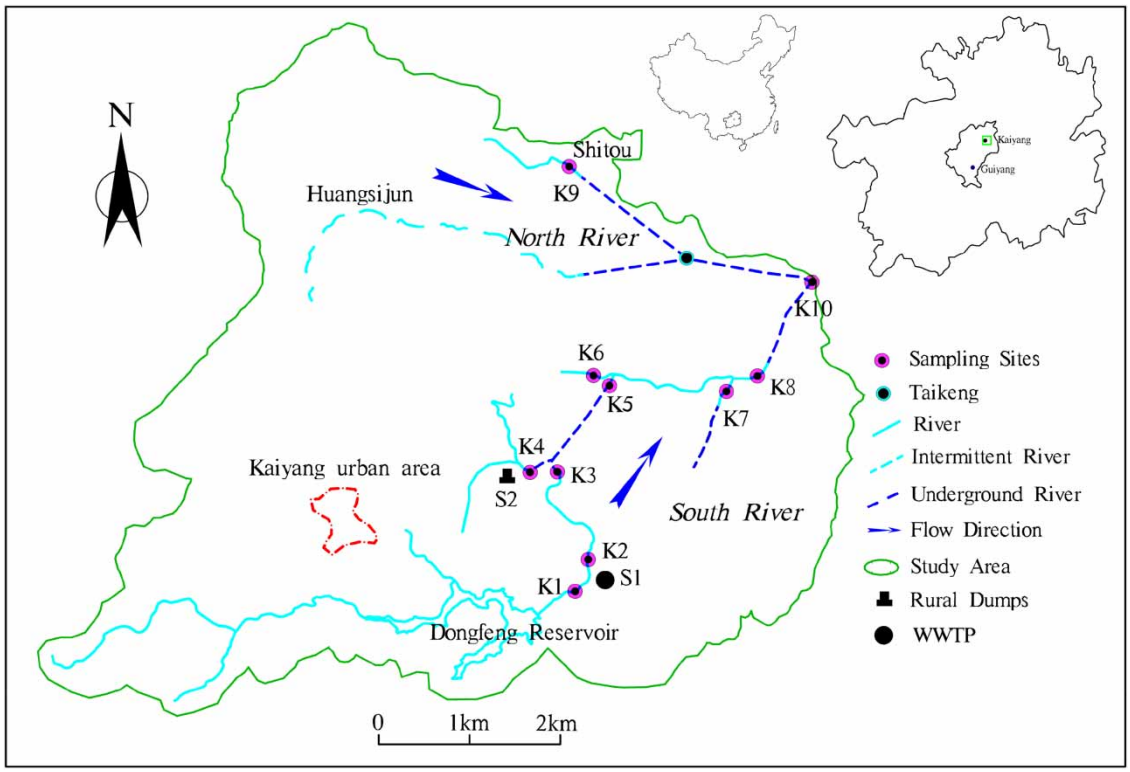


**Figure 1** | The location of the sampling sites.

collection, aqueous samples for antibiotic analysis were immediately chilled (4 °C) and transported by overnight express to Beijing Key Laboratory of Water Resources and Environmental Engineering, CUGB (Chen *et al.* 2014; Liu *et al.* 2015; 2016).

### SPE-UPLC-MS/MS analysis

An auto SPE instrument (Auto SPE-06C, Reeko Instrument, TX, USA) with an Oasis HLB SPE column (6 mL, 500 mg, Waters, MA, USA) was employed to extract antibiotics in groundwater samples. The column was activated by a 6 mL methanol and 6 mL $Na_2EDTA$ solution (0.1 g/L). After the addition of 6.0 g $Na_2EDTA$ (China National Pharmaceutical Group Corporation, Beijing, P.R. China), the pH of 1 L of groundwater sample was adjusted to 4.3–4.5 by a HCl solution and 10 μL of surrogate standards mixtures were added, then filtered through the activated SPE column at a speed of 6 mL/min. The surrogate standards mixtures were composed of ofloxacin-$D_3$ and sulfadimethoxone-$D_6$ (4 mg/L in methanol solution, Witega, Berlin, Germany). The SPE column was leached by 10 mL of ultra-pure water and dried for 30 min under $N_2$ conditions before being eluted by 6 mL ammonia/methanol (5/95, V/V) of solution. Finally, the eluent was purged to <1 mL with $N_2$. Methanol/water (1/1, V/V) was used to replenish the sample volume to 1.00 mL for analysis. The internal standards mixture of 10 μL was added to the final sample. The internal standards mixture (4 mg/L in methanol solution) was composed of difloxacin-$D_3$ (Witega, Berlin, Germany), sulfapyridine-$^{13}C_6$ (Witega, Berlin, Germany), sulfachloropyridazine-$^{13}C_6$ (Witega, Berlin, Germany), erythromycin-$^{13}C$-$D_3$ (TLC Pharmaceutical Standards, Ontario, Canada), and demethylchlortetracycline (Dr. Ehrenstorfer, Augsburg, Germany). Methanol was purchased from Merck (Darmstadt, Germany) and HCl and NaOH were purchased from Beijing Chemical Plant (Beijing, P.R. China).

The antibiotics standards were purchased from Dr. Ehrenstorfer (Augsburg, Germany) and Sigma-Aldrich (MO, USA), as shown in Table 1. All standards were dissolved in methanol to achieve a concentration of 0.1 g/L. Analysis of antibiotics in groundwater was performed by using a Waters ACQUITY UPLC H-Class system coupled with a Waters Xevo-TQ-S Triple Quadrupole MS/MS spectrometer equipped with the electrospray ionization (ESI) source (Waters, MA, USA). A Waters ACQUITY UPLC BEH C18 (2.1 × 50 mm) at 40 °C was used. The mobile phase contained 0.1% aqueous formic acid (A) and methanol/acetonitrile (B, 1/1, V/V, with 0.1% formic acid) at a 0.2 mL/min flow rate under the following gradient program: 0 min, 10% B; 0–7.0 min, 10–60% B; 7.0–7.5 min, 60–100% B; 7.5–10.0 min, 10% B. Formic acid was purchased from Sigma-Aldrich (MO, USA) and acetonitrile was purchased from Merck (Darmstadt, Germany). The MS/MS was operated in positive ion mode with the source temperature and desolvation temperature set at 120 °C and 500 °C, respectively. The cone gas flow and nebulization gas flow were set at 10 L/h and 600 L/h, respectively. Sample injection volume was 1 μL.

### Quality assurance and quality control

For quality assurance and control, two duplicated aqueous samples were collected in two random sampling sites within the study area. While conducting analysis, one laboratory blank, one spiked laboratory blank, one parallel sample, and one spiked sample matrix were added into the detection sequence. In our analysis, the recovery of surrogates (difloxacin-$D_3$ sulfapyridine-$^{13}C_6$) were 93.34% and 77.67%, respectively, and the concentrations of selected antibiotics in the laboratory blank were lower than the corresponding method detection limits. The recovery range of the spiked laboratory blank were 55–105%, except for sparfloxacin (45%) and chlorotetracycline (50%), in which their recoveries were stable at about 50% in multiple detections. The qualification rate of the parallel sample was 94.2%.

## RESULTS AND DISCUSSION

### Occurrence and levels of antibiotics

A summary of the 35 selected antibiotics in the 10 water samples of the Karst river system is presented in Table 1 and Figure 2. A total of 28 antibiotics were found and at least nine antibiotics were detected in each sample, indicating that antibiotics were widely prevalent in the Karst river system in Kaiyang, southwestern China. Moreover,

**Table 1** | Thirty-five (35) antibiotics detected in Karst river samples collected from Kaiyang

| Compounds | | CAS no. | LOQ[a] | Concentration (ng/L) ($n = 10$) | | | | SPC[e] |
|---|---|---|---|---|---|---|---|---|
| | | | | Mean | Med.[b] | Max.[c] | Min.[d] | |
| Sulfonamides | Sulfacetamide(SA) | 144-80-9 | 1.06 | 0.2 | <LOQ | 1.5 | <LOQ | 1 |
| | Sulfapyridine(SPD) | 144-83-2 | 0.29 | 6.5 | 6.2 | 11.7 | <LOQ | |
| | Sulfisoxazole(SIZ) | 127-69-5 | 1.91 | – | – | – | – | |
| | Sulfachloropyridazine(SCPD) | 80-32-0 | 0.38 | 0.4 | <LOQ | 1.7 | <LOQ | |
| | Sulfadoxine(SDO) | 2447-57-6 | 0.42 | 0.4 | 0.3 | 1.0 | <LOQ | |
| | Sulfadimethoxone(SDM) | 122-11-2 | 1.39 | – | – | – | – | |
| | Sulfameter(SMT) | 651-06-9 | 0.54 | 0.2 | <LOQ | 1.0 | <LOQ | |
| | Sulfadimidin(SMD) | 57-68-1 | 1.24 | 0.4 | <LOQ | 3.9 | <LOQ | |
| | Sulfamethizole(SMTZ) | 144-82-1 | 0.86 | 2.6 | 0.7 | 19.3 | <LOQ | |
| | ∑Sulfonamides(SAs) | | | 10.5 | 9.2 | 30.4 | 2.5 | |
| Tetracyclines | Tetracycline(TC) | 64-75-5 | 3.08 | 32.9 | 16.8 | 184 | <LOQ | 1 |
| | Chlorotetracycline(CTC) | 57-62-5 | 3.72 | 0.7 | <LOQ | 7.1 | <LOQ | |
| | Oxytetracycline(OTC) | 79-57-2 | 3.17 | 34.7 | 13.1 | 237 | <LOQ | |
| | Doxycycline(DOX) | 564-25-0 | 3.28 | – | – | – | – | |
| | ∑Tetracyclines(TCs) | | | 68.3 | 29.7 | 421 | <LOQ | |
| Macrolides | Erythromycin(ERY) | 114-07-8 | 0.68 | 45.4 | 48.2 | 103 | <LOQ | 1 |
| | Josamycin(JOS) | 16846-24-5 | 1.13 | 0.4 | <LOQ | 1.5 | <LOQ | 2 |
| | Lincomycin(LIN) | 859-18-7 | 1.06 | 274 | 287 | 861 | 5.2 | 1 |
| | Spiramycin(SPI) | 8025-81-8 | 2.99 | 2.3 | 3.1 | 4.6 | <LOQ | |
| | Roxithromycin(ROX) | 214-83-1 | 0.84 | 27.5 | 31.0 | 54.5 | 1.2 | |
| | ∑Macrolides(MLs) | | | 350 | 422 | 884 | 12.6 | |
| Quinolones | Lomefloxacin(LOM) | 98079-52-8 | 2.63 | – | – | – | – | 2 |
| | Difloxacin(DIF) | 91296-86-5 | 2.37 | – | – | – | – | |
| | Moxifloxacin(MOX) | 151096-09-2 | 2.84 | 8.5 | 8.9 | 26.9 | <LOQ | |
| | Nalidixic acid(NDA) | 389-08-2 | 1.72 | 7.2 | 6.2 | 20.5 | 2.2 | |
| | Oxolinic acid(OXA) | 14698-29-4 | 3.19 | – | – | – | – | |
| | Ciprofloxacin(CIP) | 85721-33-1 | 2.66 | 15.6 | 8.7 | 86.4 | <LOQ | |
| | Fleroxacin(FLE) | 79660-72-3 | 3.00 | 0.4 | <LOQ | 3.6 | <LOQ | |
| | Sparfloxacin(SPA) | 111542-93-9 | 2.59 | 1.4 | <LOQ | 8.4 | <LOQ | |
| | Ofloxacin(OFL) | 82419-36-1 | 4.03 | 199 | 114 | 1,200 | 5.6 | |
| | Norfloxacin(NOR) | 70458-96-7 | 4.01 | 69.4 | 30.1 | 442 | 6.5 | |
| | Enrofloxacin(ENR) | 93106-60-6 | 2.71 | 2.0 | 2.7 | 3.7 | <LOQ | |
| | Danofloxacin(DAN) | 112398-08-0 | 3.98 | – | – | – | – | |
| | Cinoxacin(CIN) | 28657-80-9 | 2.70 | 4.6 | 4.1 | 15.4 | <LOQ | |
| | Enoxacin(ENO) | 74011-58-8 | 3.97 | 7.9 | 5.6 | 34.0 | <LOQ | |
| | Flumequine(FLU) | 42835-25-6 | 0.82 | 3.0 | 0.7 | 22.6 | <LOQ | |
| | Pipemidic acid(PPA) | 51940-44-4 | 2.57 | 1.3 | <LOQ | 3.7 | <LOQ | |
| | ∑Quinolones(QNs) | | | 320 | 180 | 1,807 | 18.6 | |
| Chloramphenicol(CAP) | | 56-75-7 | 1.42 | 3.6 | 4.3 | 7.3 | <LOQ | 1 |

[a]Limit of quantification.
[b]Median.
[c]Maximum.
[d]Minimum.
[e]Standards Production Company.
1: Dr. Ehrenstorfer. 2: Sigma-Aldrich.

Lincomycin (LIN), roxithromycin (ROX), nalidixic acid (NDA), OFL, and norfloxacin were detected in all of the samples with a detection frequency of 100%. High detection frequencies of sulfapyridine (90%), oxytetracycline (OTC, 90%), ERY (90%), tetracycline (TC, 80%), ciprofloxacin (CIP, 80%), enoxacin (80%), moxifloxacin (70%), and chloramphenicol (70%) were also observed, while only seven antibiotics including sulfisoxazole, sulfadimethoxone,

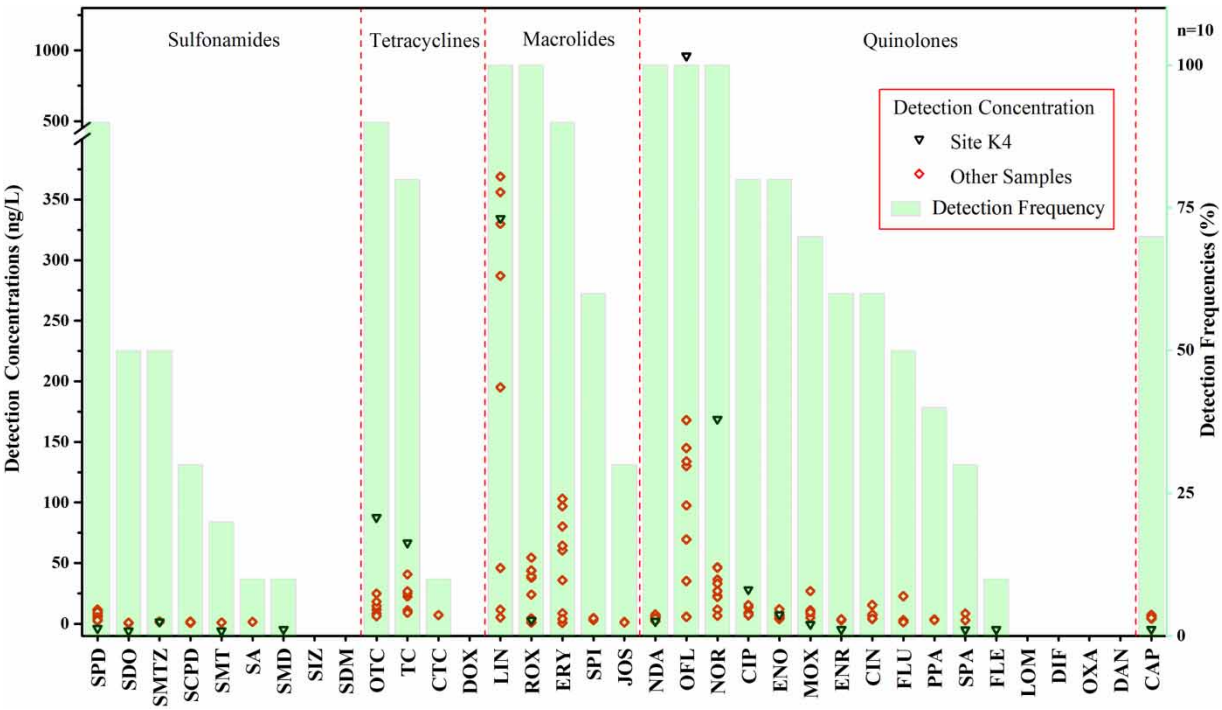


**Figure 2** | Concentration, distribution and detection frequencies of antibiotics detected in Karst river samples.

doxycycline, lomefloxacin, difloxacin, oxolinic acid, and danofloxacin were not detected. The maximum total concentration of sulfonamides (SAs), tetracyclines (TCs), macrolides (MLs), and quinolones (QNs) in each sample were 30.4 ng/L, 421 ng/L, 884 ng/L, and 1,807 ng/L, respectively. The percentages of MLs, QNs, TCs, and SAs in relation to total antibiotic concentrations were 47%, 43%, 9%, and 1%, respectively (Figure S1, available with the online version of this paper). The detected concentrations of different antibiotic types correspond with their usage quantity in southwestern China in 2013 (1390 tons of SAs, 5740 tons of MLs, and 3850 tons of QNs; Zhang *et al.* 2015).

Higher detection frequencies and concentrations of antibiotics at K4 were observed. The direct discharge of sewage from the rural dump near this sampling site may be the key reason for abnormal antibiotics contamination. The risk quotients (RQ) of 14 antibiotics on selected aquatic organisms are summarized in Table S1 (available online). There is a lower risk for plants, invertebrates, and fish being contaminated from antibiotics in the study area, however, there are significantly high RQ values of OFL (57.1), ERY (5.2), CIP (5.1), TC (2.0), and OTC (1.4) for algae.

## Spatial distribution of antibiotics

As shown in Figure 3 and Figure S2, there are similar compositions and concentrations of antibiotics at sampling sites K1 (681 ng/L) to K8 (730 ng/L), with the exceptions of K4, K6, and K7, indicating that the presence of WWTP and rural dumps in this Karst area has a negligible influence on the spatial concentration distribution of antibiotics. Even the highest detection concentrations of antibiotics at K4 (3,146 ng/L) near rural dumps was detected; however, the increased flow quantity ($Q_{river}$) of river at the downstream sampling site (80 L/s at K3 to 120 L/s at K5; Table S2) could have diluted the antibiotics and stabilized their concentration distribution (628 ng/L at K3 and 816 ng/L at K5). Especially, 11 antibiotics were detected in the rural source of drinking water (K7) with a total concentration of 45.7 ng/L, the discharge of wastewater from scattered small villages may be the key sources (Zhang *et al.* 2015). (Figure S2 and Table S2 are available with the online version of this paper.)

In order to evaluate the pollution load from sources to the Karst river system, the mass flux of antibiotics ($C_{antibiotics} \times Q_{river}$) in the study area are calculated in

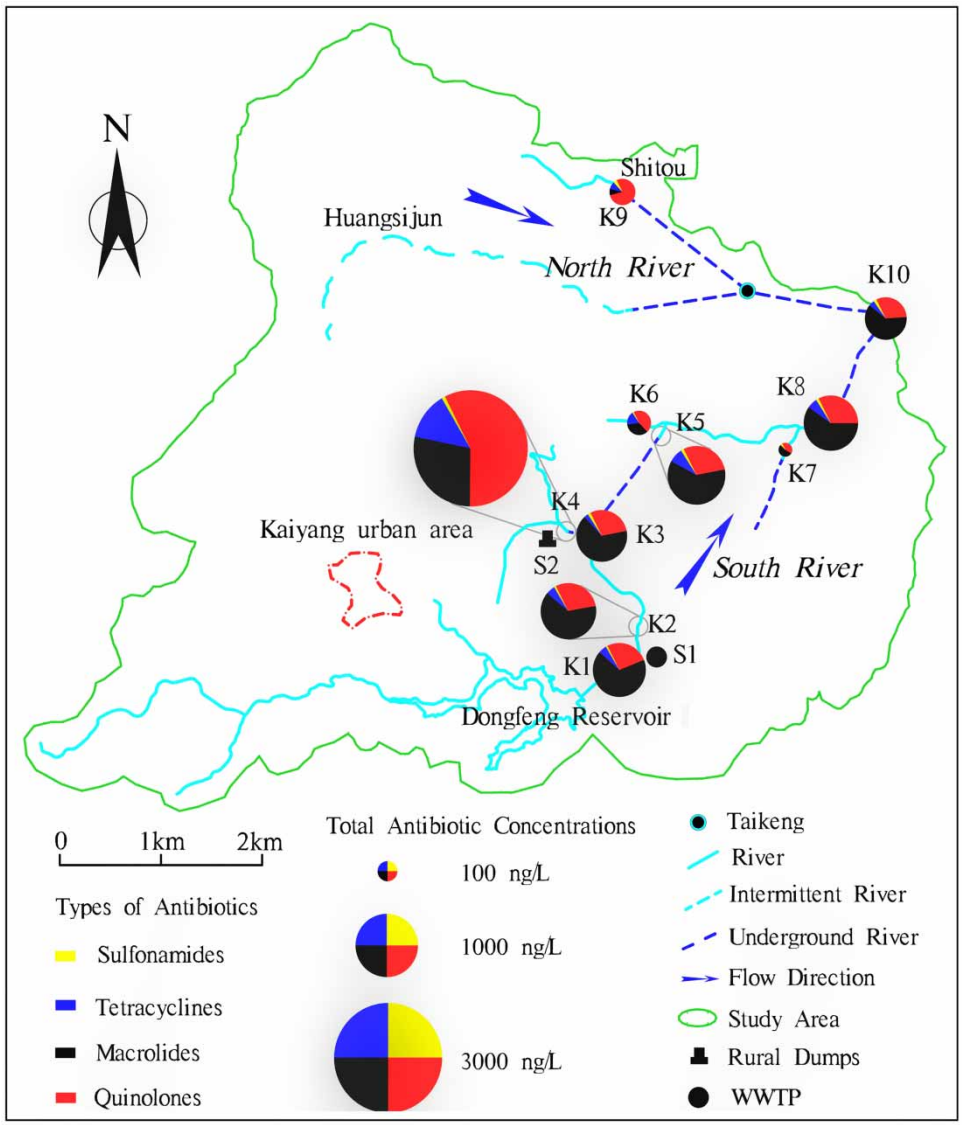


**Figure 3** | Spatial distribution of four antibiotics types in this study area.

Figure 4. The mass flux of antibiotics increases in correspondence to the flow direction in the South and North river. The presence of WWTP and the rural dump has a significant effect on the mass flux of antibiotics. In addition, poor natural attenuation of antibiotics due to the aquifer characteristics with extremely high hydraulic conductivities and short residence times also make a significant effect on the mass flux of antibiotics (Hillebrand *et al.* 2015).

As illustrated in Figure S3 (available online), the south river contains about 86% of the total detected antibiotics in this area, while the rural dumps near K4 and WWTP near K1 are the main sources of antibiotics, which account for 33% and 40% of the total detected antibiotics, respectively. Previous studies reported that conventional WWTPs were designed without consideration of highly polar pollutants removal such as antibiotics (Xu *et al.* 2007), which leads the WWTP to become a significant pollution source for antibiotics. Some prevention measures to those major sources should be conducted to control the potential risks of antibiotics for the environment, especially for the local residents.

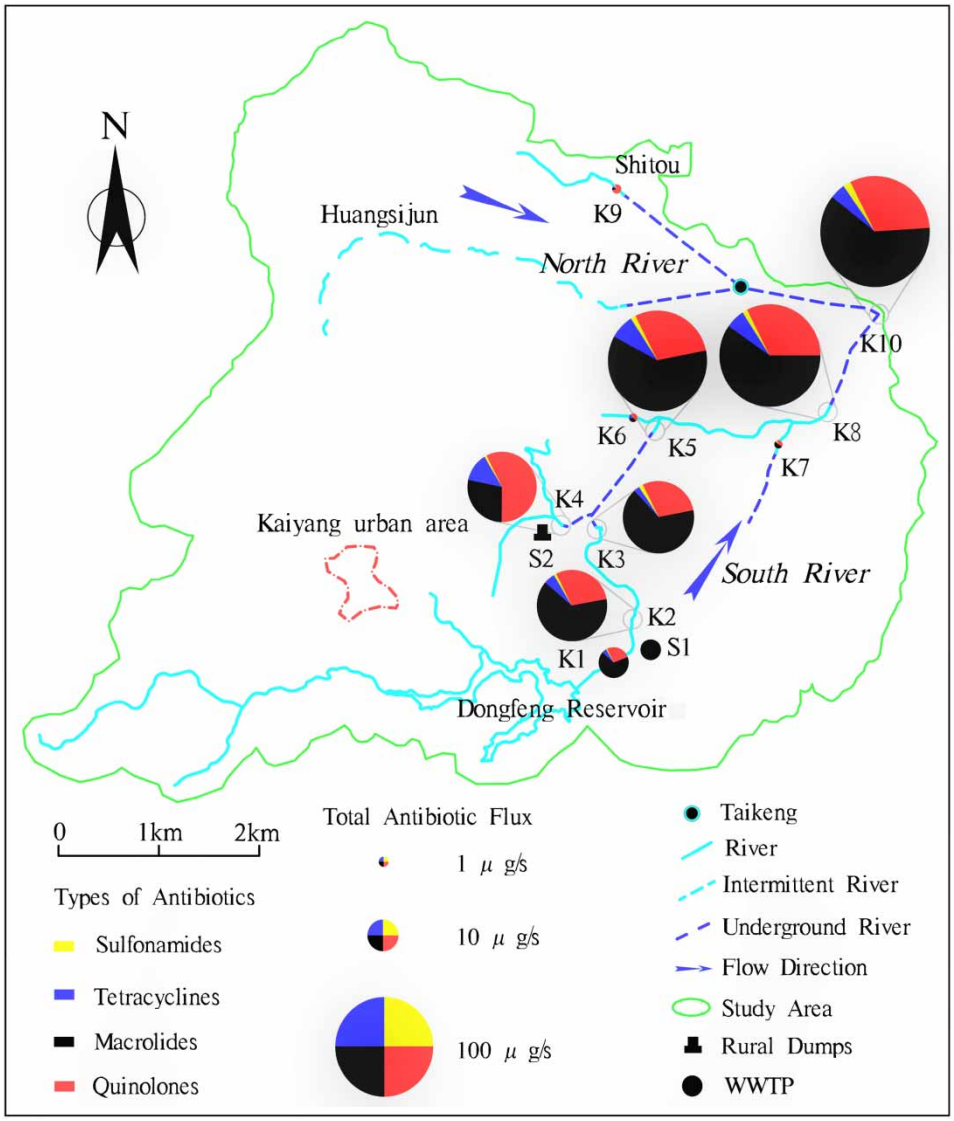


**Figure 4** | Mass flux ($C_{antibiotics} \times Q_{river}$) of four antibiotics types in this study area.

## CONCLUSIONS

This is the first study to investigate the occurrence and distribution of antibiotics in the Karst river system in Kaiyang, Southwest China. Results from this study could provide some important information for the prevention and control of antibiotic pollution in this area or in other Karst areas globally. A total of 28 target antibiotics were detected and lincomycin, roxithromycin, nalidixic acid, ofloxacin, and norfloxacin were detected in all samples with a detection frequency of 100%. Macrolides and quinolones were the dominant antibiotics, their percentage of total antibiotic concentrations being 47% and 43%, respectively. Based on the spatial concentration and mass flux distribution of four antibiotics types, the main sources of antibiotics in Karst river systems were WWTPs and rural dumps without sanitary treatment, which accounted for 33% and 40% of total antibiotics. Some prevention measures should be conducted to control the potential risks of antibiotics to the environment, especially for the local residents.

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