Journal of Contaminant Hydrology 272 (2025) 104552

Contents lists available at ScienceDirect

Journal of Contaminant Hydrology

journal homepage: www.elsevier.com/locate/jconhyd

Modelling occurrence and environmental risk of azithromycin in an intermittent river: Applying hydrological and water quality models

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ARTICLE INFO

Keywords:
Azithromycin
SWAT model
GREAT-ER model
Intermittent stream
Predicted environmental concentration
Ecotoxicological risk assessment

ABSTRACT

Antibiotics are emerging pollutants that may negatively affect river ecosystems. The present paper aims to define a modelling approach for assessing the fate of pharmaceuticals and the ecotoxicological risk in surface waters in intermittent rivers. A hydrological model (Soil and Water Assessment Tool) and a water quality model (Geography-referenced Regional Exposure Assessment Tool for European Rivers) were used in a modelling cascade application in the Canale d'Aiedda basin (S-E, Italy). Measurements of streamflow and azithromycin (AZ) concentrations were used for calibrating the models. Predicted Environmental Concentrations (PEC) of AZ in surface waters and the ecotoxicological risk were estimated. The highest AZ concentrations in the effluent of wastewater treatment plants (2553 ng L^{-1}) and in surface waters were recorded in March 2021. The monitoring and modelling results indicated seasonal changes in AZ concentrations in surface waters: in August, the PEC was one order of magnitude lower than in March. The river reaches downstream of the inlets from the WWTPs presented the highest PEC of AZ, whereas a reduction of PEC was simulated moving downstream of the inlets. The results of the ecotoxicological risk assessment showed that in March most of the river network presented a PEC of AZ higher than the Predicted No-Effect Concentration (PNEC). Coupling the two models has proven to be an effective approach to address the complex interaction between hydrology and water quality in intermittent rivers, suitable for identifying the occurrence and environmental risk of emerging pollutants, fundamental steps for their management.

1. Introduction

Anthropogenic activities and climate change are causing flow regime alterations and water quality impairment in most Mediterranean river basins (Gómez-Navarro et al., 2024). Agriculture, breeding (excessive use of fertilizers, pesticides, and veterinary pharmaceuticals), and urban and industrial wastewaters are responsible for pollutants in surface waters (OECD, 2019). The Environmental information system of the European Union (Wise-Freshwater, 2024) reported that only 38 % of the surface waters are in good or better ecological status.

Recently, pharmaceuticals have been detected in surface waters and groundwater in several Mediterranean river basins (Labad et al., 2023; Mheidli et al., 2022; Palma et al., 2020; Wilkinson et al., 2022). Antibiotics are among the most important emerging pollutants (US-EPA, 2009; Verlicchi et al., 2012). Their persistence in surface waters and river sediments may change microbial communities, altering the natural biogeochemical cycles and contributing to antibiotic resistance (Barra Caracciolo et al., 2015; Danner et al., 2019; Di Cesare et al., 2015; Shaheen et al., 2022; Verlicchi et al., 2012). Azithromycin (AZ) is one of the most widely used antibiotics in veterinary and human medicine due to its high potency and wide applicability (Vermillion Maier and Tjeerdema, 2018; WHO, 2012). Its presence in surface waters has been linked to toxic effects (Almeida et al., 2021; Grabicova et al., 2014). AZ is generally poorly removed in conventional wastewater treatment

Abbreviation: AZ, Azithromycin; SWAT, Soil and Water Assessment Tool; GREAT-ER, Geography-referenced Regional Exposure Assessment Tool for European Rivers; PEC, Predicted Environmental Concentrations; PNEC, Predicted No-Effect Concentration; WWTP, wastewater treatment plant; PE, population equivalent; NSE, Nash and Sutcliffe Efficiency; R^2, coefficient of determination; EL, emission load; ER, excretion rate; RR, removal rate; DDD, Defined Daily Dose; HRT, travel time; K, degradation constant.

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https://doi.org/10.1016/j.jconhyd.2025.104552
Received 20 January 2025; Received in revised form 5 March 2025; Accepted 24 March 2025
Available online 25 March 2025
0169-7722/

plants (WWTPs) (Grandclément et al., 2017; Verlicchi et al., 2012). Once released into the rivers, AZ is subject to dilution and attenuation processes such as biotransformation, sorption, volatilization, and photolysis that depend on water travel time within the waterbody, and the physicochemical properties of the riverbed (Patel et al., 2019).

In recent years, scientific investigations have been carried out to explore the contamination pattern of AZ (Feitosa-Felizzola and Chiron, 2009; Hanamoto and Yamamoto-Ikemoto, 2022; Wilkinson et al., 2022). However, in Mediterranean intermittent river systems, limited knowledge exists regarding the in-stream processes, and transport of AZ, compared to nutrients (Stamatis et al., 2013). Also, a few studies on the fate of AZ in different seasons or phases of river flow were carried out (Mandaric et al., 2019). Generally, intermittent streams in un-impacted conditions show a highly intra- and inter-annual variable flow regime, with low flow and zero flow in summer. These peculiarities influence sediment and chemical transport and the in-stream processes. Point source discharges may alter the natural flow regime of these rivers with a shift toward perennial conditions (Ricci et al., 2022). In the dry season, near-constant streamflow (except flash flood events) influences the nutrient and sediment in-stream dynamics with a high level of sediments and organic compounds deposition (von Schiller et al., 2017). In the wet season, high flow and floods generate riverbed sediment resuspension that may increase in-stream concentrations of chemicals (Osorio et al., 2014; Reoyo-Prats et al., 2018).

The presence of AZ in water bodies receiving direct wastewater discharge is of concern for water resources managers who need tools for predicting the fate of pharmaceuticals and assessing ecotoxicological risk. Hydrological and water quality models can be valid tools for predicting environmental concentrations of pollutants and risk assessment since they integrate hydrological and water quality data formalizing the processes to which chemicals are exposed in the river network (Grill et al., 2016; Jagiello et al., 2015; Keller, 2006; van Leeuwen and Vermeire, 2007).

Several models were developed and implemented to predict the fate of emerging pollutants in surface waters (Addis et al., 2023; Datta et al., 2018; Fox et al., 2000; Hao et al., 2015; Holt et al., 2003; Schulze and Matthies, 2001; Schowanek and Webb, 2002; Zhang et al., 2015). However, the literature does not include modelling applications focusing on the fate of pesticides and pharmaceuticals in intermittent streams. Currently, the knowledge is not sufficient to support specific management actions. The limited hydrological data availability, which characterizes these river systems, is the major limitation for the model applications in the Mediterranean Region (De Girolamo et al., 2022).

This study's general objective was to develop and test a modelling approach for assessing the fate of pharmaceuticals in surface waters in basins with limited data availability and intermittent river systems. The specific aims were: i) to predict the contamination of AZ, an antibiotic coming from point sources; and ii) to assess the ecotoxicological risk in the surface waters at the basin scale. To this aim, hydrological and water quality modelling tools were used in a cascade approach and tested in the Canale d'Aiedda basin (Apulia Region, Italy). Specifically, the Soil and Water Assessment Tools model (SWAT, Arnold et al., 1998) was run to generate daily streamflow in the river reaches constituting the river network. Modeled streamflow and field observations were successively used as input in the "Geography-referenced Regional Exposure Assessment Tool for European Rivers" (GREAT-ER), one of the most important chemical exposure prediction models (Feijtel et al., 1997; Kehrein et al., 2015) to predict the environmental fate of pharmaceutical, which is generally applied with a stochastic procedure because of the lack of hydrological and hydraulic data (Aldekoa et al., 2013). The approach proposed in this study makes it possible to overcome this limitation by allowing users to apply GREAT-ER in a deterministic way to identify the river reaches that are really at ecotoxicological risk.

This study may improve watershed management in the Mediterranean Region and increase knowledge concerning the emerging pollutants in intermittent streams.

2. Material and methods

2.1. Study area: Canale d'Aiedda Basin (Italy)

The study area is the Canale d'Aiedda catchment (Apulia Region, Southern Italy). In the river basin, the climate is typically Mediterranean: the mean annual rainfall recorded from 1920 to 2012 was 855.9 mm y^{-1} and 576.2 mm y^{-1} in the mountainous and lowland areas, respectively (Centanni et al., 2024). Limestone lithology characterizes part of the basin, therefore, the area effectively contributing to surface runoff is 222 km^2 (Fig. 1) (Ricci et al., 2023). The stream feeds the European-protected wetland (Palude la Vela) belonging to the Mar Piccolo, a Site of Community Importance (SIC-IT9130004).

The high spatial variability that characterizes environmental factors such as rainfall and lithological and geological features influence the hydrological regime, and the point source discharges are responsible for flow regime alterations (Ricci et al., 2022). Three wastewater treatment plants (WWTPs) discharge treated wastewaters into small first-order tributaries (Fig. 1): Montemesola (WWTP1; 7000 population equivalent – PE, resident population 3.608; mean discharge 0.013 $m^3\ s^{-1}$), Monteiasi (WWTP2; 49,566 PE; it includes the municipality of Grottaglie, resident population 36,246; mean annual discharge 0.101 $m^3\ s^{-1}$), and San Giorgio Ionico (WWTP3; 32,164 PE, mean yearly discharge 0.055 $m^3\ s^{-1}$; resident population 14,355). Sporadic isolated houses, not connected to the WWTPs, are present in the area but their contribution is negligible. Downstream of the inlet from WWTPs, the flow regime is perennial. Indeed, the river network is a longitudinal continuum where perennial, intermittent and ephemeral river reaches coexist.

Agricultural lands cover about 90 % of the area, with vineyards (36.3 %), olive groves (24.5 %), and cereals (28.1 %). Natural areas with coniferous forests (2.7 %), Mediterranean maquis (2.4 %), and bushes (0.9 %) are also present (D'Ambrosio et al., 2020). In the area, there aren't intensive livestock farms.

2.2. Field measurements

Measured daily streamflow recorded at two gauging stations (A and B in Fig. 1). were used to calibrate the hydrological model (for more information about the instruments refer to D'Ambrosio et al., 2019). Two sampling campaigns were carried out to detect the presence of AZ in surface waters: March 2021, and August 2021, far from flood events. Both in March and August, no rainfall was recorded during the day of sampling and the day before, therefore it can be assumed that the WWTP was the unique source of AZ and that no overflow occurred. Daily streamflow was about 0.060 $m^3 s^{-1}$ both in March and August and it was due to the WWTP discharge. Streamflow upstream WWTP was absent on both sampling days. Indeed, this river reach in un-impacted condition is ephemeral, surface runoff occurs only during flood events.

For each sampling campaign, samples were taken in surface water upstream of the emission point WWTP3 (Em, in Fig. 2), in four river sections downstream of WWTP3 (EV, EV1, EV2, EV3 in Fig. 2), and on the effluent. Samples were transported in a refrigerated container and stored (−20 °C) until the extraction. The selected river segments were homogeneous, and no factors potentially altering hydrology were present (i.e. inflow, water diversions, or precipitation events).

Measurements of water flow velocity were taken by using the portable flow meter (ISCO 750 Area-Velocity Flow Module) and integrated to obtain an average flow velocity across the river section. Water depth measurements were taken in the same river sections where flow velocity was recorded.

Surface water samples (500 mL) were filtered with 0.7-μm glass microfiber filter GF/F from Whatman (UK) and were passed through a multi-layered and multi-sorbent solid phase extraction (SPE) cartridge. The extracts were analyzed by liquid chromatography (LC) coupled to a high-resolution mass spectrometer, Q-Exactive Orbitrap (Thermo-Fisher Scientific, Germany). The method used was developed by Gómez-

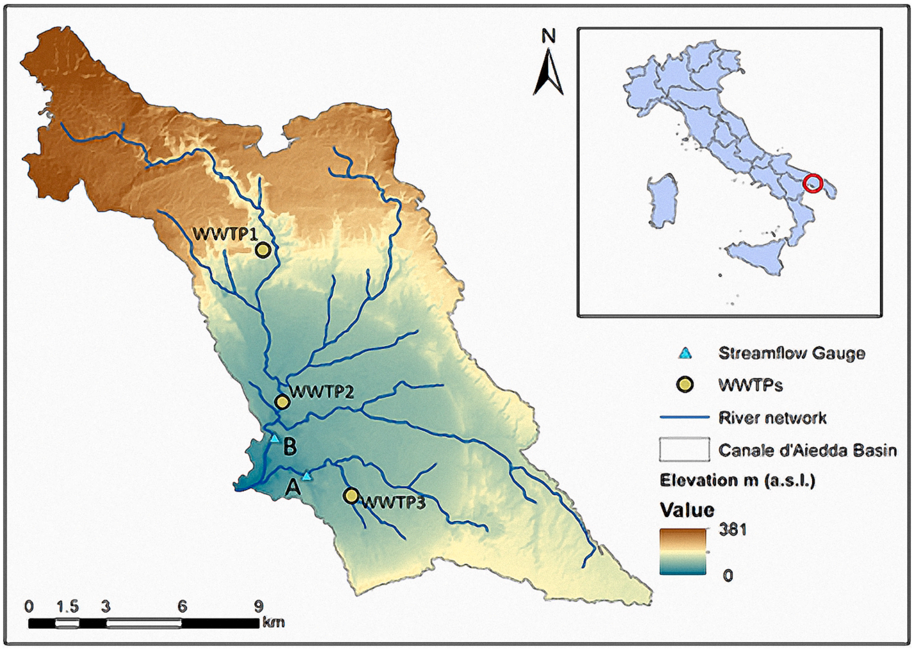

Fig. 1. Study area: Canale d'Aiedda (Italy). WWTP1 is for treatment plant of the municipality of Montemesola, WWTP2 is for Monteiasi-Grottaglie, and WWTP3 is for San Giorgio Ionico.

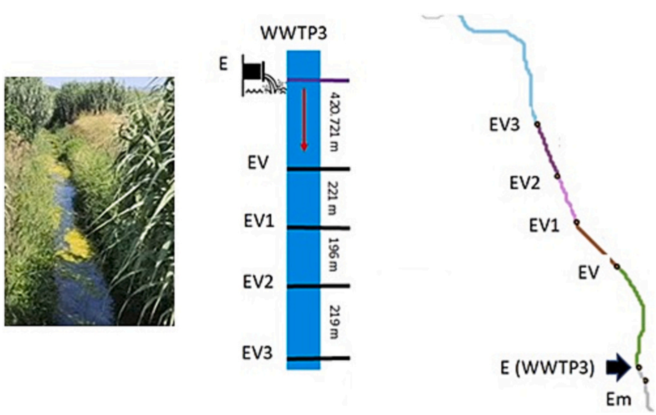

Fig. 2. Sites of samplings along the Canale d'Aiedda stream (Italy). WWTP3 is for wastewater treatment plant of the San Giorgio Ionico municipality.

Navarro et al. (2023) for surface water samples. The extracts were analyzed in positive electrospray ionization mode (ESI+). LC-separation was performed using ultra-high-performance liquid chromatography in a Waters Acquity HSS T3 (C18) column (100 × 2.1 mm i.d., 1.8 μm particle size) thermostated at 40 °C using a Waters ACQUITY UHPLC system (Waters, Milford, MA). The adopted mobile phases were 100 % acentonitrile (solvent A) and 5 mM AcNH4+ 0.1 % formic acid in water (solvent B). The gradient applied was 5 % A for 0.3 min then ramped to 30 % A from 0.3 to 10.0 min, followed by 65 % A from 10.0 to 13.3 min, 100 % from 13.3 to 15.5 and held at 100 % A from 15.5 to 17.3 min. The column was re-equilibrated at 5 % A for 1.3 min before the next injection. The total run for each sample was 19 min. The injection volume was set to 10 μL. As for the mass spectrometer, a full-scan followed by a targeted data-independent acquisition (targeted-DIA) mode was used with a specific predefined inclusion list, where the exact mass of the selected precursor ion, optimized retention time windows, and optimized collision energies were set to obtain high-quality MS2 product ions. AZ was detected and quantified using both standards and internal standards with limits of detection (LOD) and quantification (LOQ) of 0.34 and 1.14 ng L^{-1}, respectively. No repetitions were carried out for each sample.

2.3. Conceptual model

In this work, an approach for modelling the fate of pharmaceuticals from point sources in ungauged intermittent streams was defined (Fig. 3). The SWAT model version 2015 (Arnold et al., 1998) and the GREAT-ER model (Feijtel et al., 1997) were implemented in a modelling cascade application in the Canale d'Aiedda basin (Apulia, Italy). The river network was subdivided into river reaches and daily streamflow simulated by the SWAT model for each of the river reaches was used as input in the deterministic version of the GREAT-ER model (basic version 4.1) (Kehrein et al., 2015; Schowanek et al., 2001) to simulate the fate of AZ, an antibiotic whose presence in the surface waters of the Canale d'Aiedda basin has been constantly detected in the sampling campaigns.

SWAT is a hydrological model (Arnold et al., 1998) widely used to simulate streamflow (Leone et al., 2024), sediment (Lucas-Borja et al., 2020), and nutrient loads (Ricci et al., 2022) in gauged and ungauged river basins (Arnold et al., 2012).

GREAT-ER (Feijtel et al., 1997) estimates the Prediction Environmental Concentrations (PECs) of chemicals in each of the river segments preventively defined by simulating the release of chemicals into the river network, their degradation and migration along the water flow direction. It assesses the ecotoxicological risk related to the presence of chemicals in surface water by comparing the PEC with a reference threshold value (Aldekoa et al., 2013; Cassani et al., 2001; Kehrein et al., 2015; Lämmchen et al., 2021). To select this reference threshold value, we adopted the criteria reported by Carvalho et al. (2016) in the report "Monitoring-based Exercise: Second Review of the Priority Substances List under the Water Framework Directive", where the authors suggested assuming long-term toxicity effects to short-term toxicity effects and to follow a conservative approach. The "Predicted No-Effect Concentration" (PNEC), which is defined as the concentration of a substance at or below which adverse effects on ecosystems are not likely to occur at any exposure time, was selected as the reference threshold value. The PNEC was assumed to equal 0.019 μg L^{-1} as indicated by Loos et al. (2018) in the technical report "Review of the 1st Watch List under the

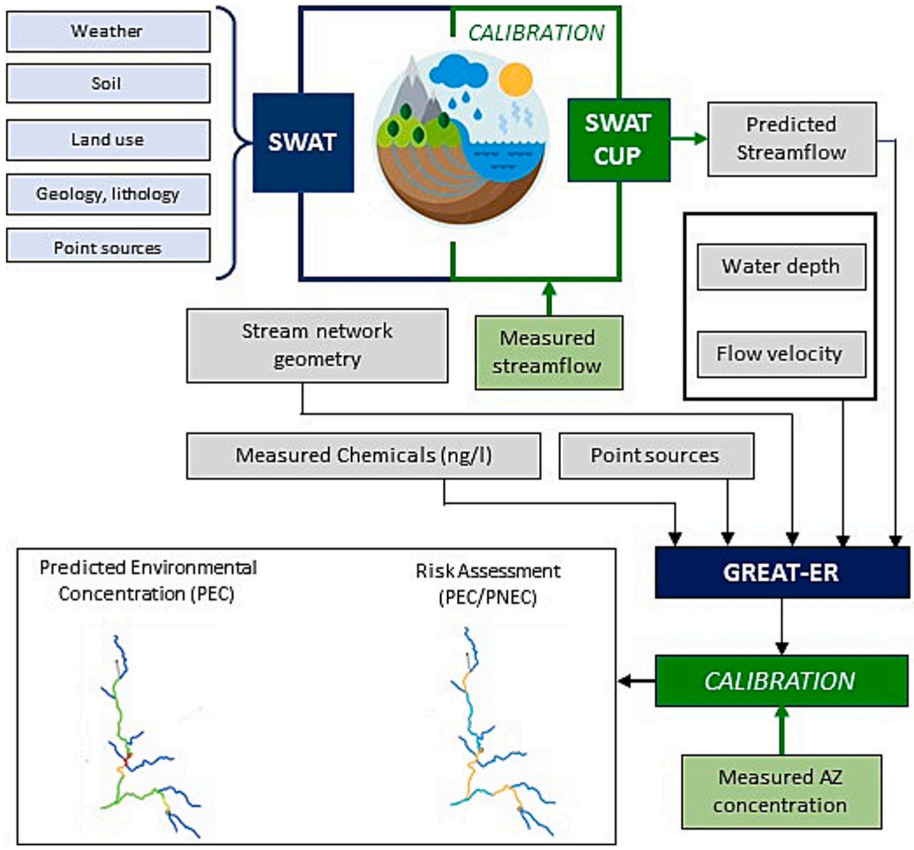

Fig. 3. Scheme of the SWAT and GREAT-ER application in a modelling cascade mode.

Water Framework Directive and Recommendations for the 2nd Watch List". If PEC/PNEC<1, the risk is acceptable. The risk assessment maps developed for the study area identify the river segments where the concentration of the pharmaceutical is expected to be higher than the fixed threshold. In the present work, the maps of the PEC and the risk assessment were designed for each sampling campaign (March 2021; August 2021).

2.3.1. SWAT model implementation and calibration

Several input data were collected and processed (Table 1), for more details refer to D'Ambrosio et al., 2019. The model was set up to run at the daily time step from 2014 to 2021, using the first 3 years as a warm-up. The whole basin was divided into 40 sub-basins (threshold of 350 ha), selecting threshold values of 10 % for land use and soil class, and 20 % for slope to define 271 Hydrological Response Units.

Table 1
Input data used for modelling hydrology.

Input data	Data source and their resolution
Digital Terrain Model (DTM)	http://www.sit.puglia.it, 8 × 8 m
River network	http://www.sit.puglia.it
Land use map	http://www.sit.puglia.it, 100 × 100 m; 23 land use classes
Soil database	Puglia Region (ACLA); 250 × 250 m. European Soil Data Centre (ESDAC; https://esdac.jrc.ec.europa.eu/resource-type/datasets), 500 × 500 m; 9 soil profiles
Point sources	Agenzia Regionale per la Prevenzione e Protezione Ambientale (http://www.arpa.puglia.it); Acquedotto Pugliese, annual volumes of treated sewage for each plant; 3 WWTPs
Meteorological data	http://www.protezionecivile.puglia.it; Agenzia Regionale per le Attività Irrigue e Forestali della Puglia (https://www.arifpuglia.it), 18 meteorological stations, daily data
Agricultural practices	Farmers' and dealers' interviews

For assessing potential evapotranspiration, the Hargreaves method was adopted (Hargreaves, 1975) and to evaluate surface runoff the Soil Conservation Service-Curve Number method (United States Department of Agriculture–Soil Conservation Service (USDA-SCS), 1972) was selected. In the model setup, the point source discharges, and agricultural management practices were included.

The sensitivity analysis and the automatic calibration process were performed by using the SWAT-CUP tool choosing the Nash and Sutcliffe Efficiency (NSE) as the objective function (≥ 0.5) (D'Ambrosio et al., 2020) and selecting the "Sequential Uncertainty Fitting-2" algorithm developed by Abbaspour (2015). The model was calibrated at two gauging stations (A and B, Fig. 1) comparing simulated and daily measured streamflow (August 2017 to December 2019). To assess the SWAT model performances, the coefficient of determination (R^2), NSE, and Percentage Bias (PBIAS, %) were adopted (Moriasi et al., 2007).

2.3.2. GREAT-ER model implementation and calibration

The GREAT-ER model simulates the in-stream loss process of the chemicals (Kehrein et al., 2015) based on the emission loads (ELs; Eq. (1)). For quantifying the ELs, the model requires input data such as the domestic consumption (DC), resident population, excretion rate (ER) and removal rate (RR) in the WWTPs.

$$EL = Population \times DC \times ER \times (1 - RR) \tag{1}$$

In the present work, the ER of AZ was assumed 63 % of the consumption (National Center for Biotechnology Information, 2023). The RR of AZ mainly depends on the WWTP technology, the literature reports a wide range of values (Mirzaie et al., 2022). The WWTPs of the study area are activated sludge plants, for which Tran et al. (2016) reported ER from 49 % to 81 %, similar values (50 % to 85 %) were reported by Pan and Yau (2021). DC estimation is based on the Defined

Daily Dose (DDD), which is the average maintenance dose per day for drug used for adults (WHO, 2025; https://www.who.int/tools/atc-ddd-toolkit/about-ddd). Only one DDD is fixed per drug. DDD is an average value, therapeutic doses could be different depending on many factors (i.e. age, severity of disease weight). Hence, DDD gives a rough estimation of the consumption of drugs that could differ from the actual use (WHO, 2025). In Italy, the report, which summarizes the use of medicines at the national level and for the macro regions, reported a wide range of antibiotics consumption (Osservatorio Nazionale sull'impiego dei Medicinali, 2023). In 2021, the average yearly DC of AZ (kg inhabitant^{-1} y^{-1}) for Southern Italy was 1.8 (DDD) per 1000 individuals per day; with DDD for AZ = 0.3 g (https://www.aifa.gov.it/documents/20142/1853258/Rapporto_Antibiotici_2021.pdf; Table 2.17 page 81), corresponding to $1{,}971 * 10^{-4}$ kg inhabitant^{-1} y^{-1}. However, it is important to highlight that antibiotic consumption is not constant throughout the year (Shaheen et al., 2022) and, during the first and second wave of the COVID-19 disease, an increase in AZ consumption was recorded. Gagliotti et al. (2024), in their study "Use of azithromycin attributable to acute SARS-CoV-2 Infection", reported increases in domestic consumption of AZ up to 33.03 DDD per 1000 individuals per day from February 2020 to February 2022 compared with a previous control period. Hence, DC was presumably higher than the average annual value during the second wave of the coronavirus disease (in the study area, it occurred in March 2021). In addition, it is also plausible that in March 2021, when there was a lockdown, the actual resident population was higher than in August 2021. For these reasons, the EL was calibrated using AZ concentration measurements at the effluent. The calibration was carried out by applying the Montecarlo simulation (5000 runs) where each parameter in Eq. (1) varied within a predefined interval. It was assumed: an annual resident population of ±10 %, RR from 40 % to 85 % (Pan and Yau, 2021), and DC from 0,6 to 33 DDD per 1000 individuals per day (Gagliotti et al., 2024). ER was assumed to be constant (63 %). For the GREAT-ER simulation, we selected the values of DC, RR and Population that produced the EL (Eq. (1)) value close to the measured ones at effluent in March and August, respectively. DC, RR, and ER were assumed to be the same for all WWTPs in the basin. This is a plausible assumption, but it should be noted that results may be affected by a large uncertainty.

For the instream processes, the model needs hydrological and hydraulic data

such as flow velocity (Velocity_mean, Velocity StdDev, 5th percentile, 50th percentile) and flow depth (Depth_mean, Depth StdDev, 5th percentile, and 50th percentile), which were defined based on field measurements and simulated streamflow. Hydrological data such as mean daily streamflow, standard deviation, minimum streamflow, 5th, and 50th percentiles were derived from the SWAT model results. Simulations were carried out for March and August using monthly hydraulic and hydrological data.

Downstream from the inlet of WWTP discharge, along the river reach, the AZ may undergo different processes such as degradation, volatilization, and sedimentation. The GREAT-ER model assumes a first-order removal rate based on the following equation (Eq. (2))

$$R = 1 - e^{-(HRT*K)} \tag{2}$$

Where:

HRT is the travel time (h) in the river reach, which is a function of reach length (m) and flow velocity (m s^{-1});

K is the degradation constant of the chemical contaminant (h^{-1}).

In this study, HRT was calculated for each reach by dividing the distance [reach length (m)] by the average flow velocity (m s^{-1}) because of the field survey, and K was calibrated by using measured AZ concentrations. An initial value of the K factor was assumed (0.37 h^{-1}) (Hanamoto et al., 2018) both for March and August, after that it was manually calibrated with a "trial and error" procedure by comparing simulated and measured concentrations at the river sections downstream of the WWTP3 (EV, EV1, EV2, EV3).

3. Results

3.1. Field measurements

Upstream of the inlet (Em in Fig. 2), AZ concentration was not detected (March) or was below the limit of quantification (August). At the WWTP3 effluent, measured AZ was 2553.0 ng L^{-1} in March and 282.5 ng L^{-1} in August (Fig. 5). A decrease in AZ concentration was recorded in both sampling campaigns moving downstream of WWTP3 (EV, EV1, EV2, EV3 in Fig. 2). Specifically, it ranged from 638.2 ng L^{-1} to 148.9 ng L^{-1} in March, and from 141.6 ng L^{-1} to 13.4 ng L^{-1} in August. The minimum daily streamflow observed in summer was 0.008 m^{3}s^{-1} and 0.007 m^{3}s^{-1} at gauge A and B, respectively. This streamflow was due to the upstream WWTPs discharges.

3.2. SWAT model calibration results

Statistical performances for hydrological calibration on the daily time scale were "satisfactory" and "good" based on the criteria reported by Moriasi et al. (2007): NSE was 0.47 and 0.71 for gauges A and B, respectively, and R^2 was 0.48 and 0.72 for gauges A and B, respectively. An analysis of the results at the daily time scale showed that streamflow was overestimated at gauge A (PBIAS = −4.21) and underestimated at gauge B (PBIAS = +5.05). SWAT underestimated the normal flow and overestimated the low flow (Fig. 4). The model results showed a near-constant value for the low flow. This result was because the volumes of treated sewage for each plant were constant in the model setup since only annual volumes of treated wastewater were available (Fig. 4 Gauge A).

The sensitivity analysis showed that the most sensitive parameters were related to low flow and peak flow, as reported in Table 2 (Centanni et al., 2024). These results confirmed the difficulties in simulating daily streamflow in intermittent streams.

3.3. Predicted environmental concentrations and risk assessment

After the calibration of the factors influencing the EL (DC, RR and resident population; Table 3), the predicted AZ concentration at the effluent was in good agreement with the measured values (in March, the measured AZ was 2553 ng L^{-1} and the predicted was 2590 ng L^{-1}; in August, the measured AZ was 282.5 ng L^{-1} and the predicted was 283 ng L^{-1}; Table 3). The Uncertainty associated with the AZ concentration in the treated wastewater is very high and is mainly due to the DC (Table 3).

Concerning the calibration of the K factor, the statistical performances of modeled AZ concentrations versus measured values were satisfactory: R^2 was 0.91 and 0.82 and SRS (ratio of the RMSE and standard deviation of measured data) was 0.27 and 0.26 in March and August, respectively. The best values of K factor were 1.8 h^{-1} and 0.8 h^{-1} in March and August, respectively. The spatial pattern of the modeled AZ concentration matched quite well the measured values. However, modeled concentrations are slightly higher than measured values both in March and August. In March, measured AZ was one order of magnitude higher than in August, modeled values showed a similar pattern (Fig. 5).

Upstream of WWTP1 and WWTP3, PEC was zero in March and August (Fig. 6). Downstream of WWTP2, which was the largest plant, GREAT-ER simulated the highest PEC value. Moving downstream of the inlets a reduction of PEC was simulated. In August, the PEC was about an order of magnitude lower than in March (Fig. 6).

The river downstream of the inlets from WWTPs showed a high ecotoxicological risk associated with AZ (Fig. 7). In March, most reaches showed the PEC much higher than the PNEC. As expected, the reaches upstream of the WWTPs were not at risk (Fig. 7).

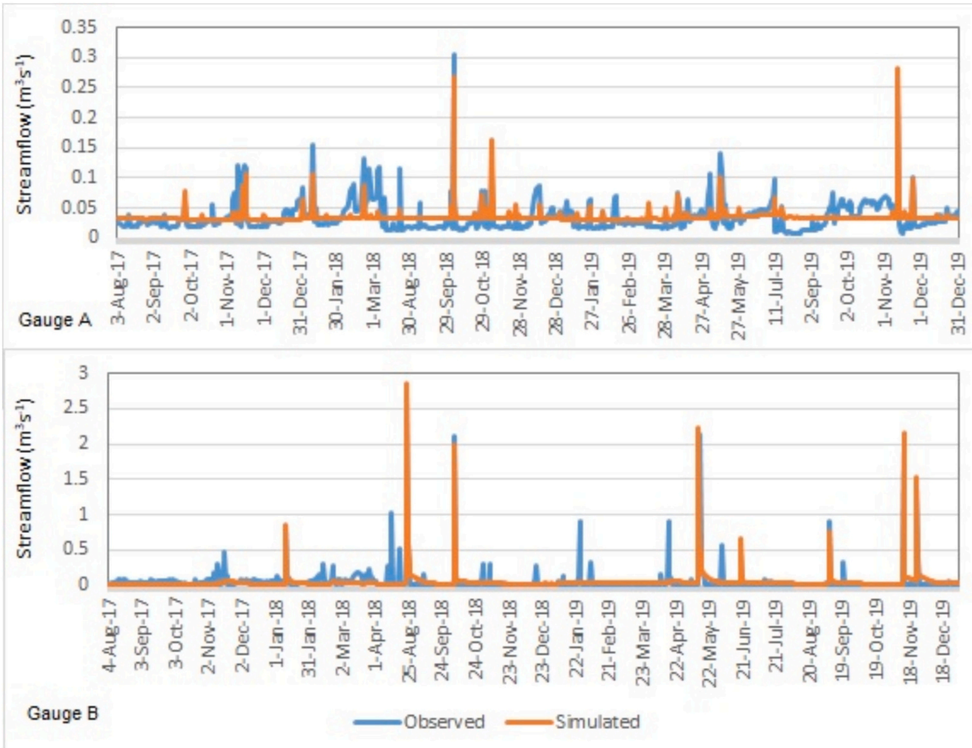

Fig. 4. Simulated and observed streamflow at the Canale d'Aiedda (Italy) Gauge A and Gauge B in Fig. 1.

4. Discussion

4.1. Field measurements: azithromycin in treated wastewater and receiving surface waters

In the Canale d'Aiedda stream, the monitoring campaigns revealed the presence of AZ in a wide range of concentrations depending on the timing of samplings. Rodriguez-Mozaz et al. (2020) for effluents from urban WWTPs localized in Europe reported a wide range (45.2–597.5 ng L^{-1}). Concerning this study, it is important to underline that the highest AZ concentrations in surface waters were recorded in March 2021, when the recorded AZ concentration in the effluent was maximum, corresponding to the second phase of the coronavirus disease (COVID-19). The results confirmed the findings from several studies that reported an increase in antibiotic consumption during the pandemic period compared to the previous years (Cappelli et al., 2022; Fukushige et al., 2022; Mohamad et al., 2022; Morales-Paredes et al., 2022). Indeed, AZ was found one of the top five most-used antibiotics during COVID-19 (Cong et al., 2022).

The AZ concentration measured downstream of the WWTP3 in March 2021 varied from 638,2 ng L^{-1} to 148,9 ng L^{-1}. These values were higher than AZ recorded in March 2016 (0–400 ng L^{-1}) in an urban and periurban area of Central Italy (Cardini et al., 2021) and were in the range reported by Sanseverino et al. (2018) for European inland surface water (maximum values below 1 μg L^{-1}). In surface water all over the world, Sanseverino et al. (2018) reported the maximal AZ concentration slightly higher than 10 μg L^{-1}. High values of AZ concentration were reported in the MENA Region (Mheidli et al., 2022).

Downstream of the WWTPs, measured AZ concentration in surface waters is strongly influenced by the WWTPs discharge and EL: in March AZ concentration was higher than in August. The AZ concentration decreased from 638.2 ng L^{-1} to 148.9 ng L^{-1} in March and from 141.6 ng L^{-1} to 13.4 ng L^{-1} in August over a distance of 636 m. Hanamoto et al. (2018) in their study reported that AZ was attenuated by 92 % in the Thames River stretch (8.3 km), and they attributed the in-stream attenuation to sediment sorption capacity, which was very high (Hanamoto et al., 2018). Feitosa-Felizzola and Chiron (2009) pointed out that the sorption to suspended sediment may be an important process of in-stream attenuation and, therefore, sediments may be a source of AZ during high-flow conditions when a resuspension of sediments occurs. However, Archundia et al. (2018) reported that no abatement in the wet season is due to runoff and remobilization processes. In the Canale d'Aiedda, further studies are needed to estimate AZ concentration in sediment and to investigate the instream processes.

4.2. Modelling streamflow by using the SWAT model

The SWAT model overestimated daily streamflow at gauge A and underestimated streamflow at gauge B. Several authors highlighted the difficulties in modelling extremely low flow and the absence of flow in the Mediterranean basin and that a large uncertainty may affect predicted streamflow (De Girolamo et al., 2022). Ricci et al. (2022) pointed out that physical and hydrological factors of the areas upstream of the gauges and the model structure influence the model performances. The authors highlight that the fraction of transmission losses from the main channel to the aquifer (TRNSRCH.bsn) is one of the most sensitive parameters in Mediterranean basins. It may assume a unique value at the basin scale, therefore, the average value adopted in this study resulted in an overestimation for the sub-basins upstream of gauge A and slightly underestimated for gauge B. In addition, input data such as the weather data (e.g. number, and location of the stations) and the volumes of treated sewage for each plant, which were considered constant due to the limited data availability, may greatly influence the results.

Despite the limitations reported above, the model proved to be a useful tool for generating long-term simulated data of streamflow, which can be used as input for further studies.

Table 2
Calibrated parameters: best fit simulation at the gauge A and B. Type of operation (in SWAT-CUP): v is for "replacement" of the initial value with the value reported in the "best fit"; r means that the initial value is multiplied by 1 + the value reported in "best fit".

Parameter	Description	Type	Best fit (A)	Best fit (B)
CH_K2.rte	Hydraulic conductivity in main channel alluvium (mm hr^{-1}).	v	7.016	43.230
SOL_AWC.sol	Available water capacity of the soil (mm H_2O mm $soil^{-1}$).	r	0.216[a,e]	−0.100[a,e]
CN2.mgt	Initial SCS Curve Number for Antecedent Moisture Condition (AMC) II	r	−0.259[b,e]	0.210[b,e]
TRNSRCH.bsn	Fraction of transmission losses from the main channel that enters the deep aquifer.	v	0.526	0.526
CH_K1.sub	Effective hydraulic conductivity in tributary channel alluvium (mm hr^{-1}).	v	107.085	29.668
SOL_K.sol	Saturated hydraulic conductivity (mm hr^{-1}).	r	0.078[c,e]	−0.107[c,e]
SOL_Z.sol	Depth from soil surface to bottom of layer (mm).	r	0.096[d,e]	−0.234[d,e]
EPCO.hru	Plant uptake compensation factor.	v	0.511	0.893
GW_DELAY.gw	Groundwater delay time (d).	v	43.824	42.052
RCHRG_DP.gw	Deep aquifer percolation fraction.	v	0.102	0.852
EVRCH.bsn	Reach evaporation adjustment factor.	v	0.865	0.865
CANMX.hru (GRBN)	Herbage maximum canopy storage (mm).	v	2.371	2.223
CANMX.hru (OLIV)	Olive maximum canopy storage (mm).	v	4.259	5.367
REVAPMN.gw	The threshold depth of water in the shallow aquifer above which the water movement from the shallow aquifer to the unsaturated zone is allowed.	v	749.153	410.453

[a] The initial SOL_AWC values were set between 0.097 and 0.130 mm H_2O/mm soil depending on the soil layer type.
[b] The initial CN2 values were set between 63.7 and 89.2, depending on the land use and soil type.
[c] The initial SOL_K values were set between 0.065 and 27.8 mm/h depending on the soil layer type.
[d] The initial SOL_Z values were set between 400 and 2000 mm depending on the soil layer type.
[e] Values multiplying the parameter in the SWAT-CUP (1+ best fit) "relative" methodology.

Table 3
Factors influencing the emission load (EL), observed and estimated AZ concentrations of treated discharged into the river, uncertainty: Interquartile range (IQR) expressed as a percentage of the median.

	March 2021	August 2021	median	Uncertainty IQR (expressed as percentage of median)
Resident Population	15,790	12,919	14,369	10.16 %
DC (kg ab^{-1} y^{-1})	0.001069	0.000142	0.001829	96.65 %
RR (%)	49	51	62.52	35.15 %
Observed AZ concentration of treated (ng L^{-1})	2553	282	3105	179.97 %
Estimated AZ concentration of treated after calibration (ng L^{-1})	2590	283	3105	179.97 %

4.3. *Predicted environmental concentrations and risk assessment of azithromycin by using the GREAT-ER model*

In this study, the GREAT-ER model was implemented in a deterministic way. Most of the case studies reported in the literature refer to stochastic procedures. The limited availability of hydrological and hydraulic data is the main limitation in the deterministic model applications (Aldekoa et al., 2013). This study showed that a preliminary application of the SWAT model, which provides hydrological data at the reach scale, allows overcoming the limited hydrological data availability and may provide a more accurate quantification of PEC and ecotoxicological risk in surface waters. This approach makes it possible upscaling local monitoring and modelling into a basin-wide model, minimizing the sample collection and data analysis costs. The methodology can be used when the environmental factors and the WWTP technology are similar within the basin. However, it should be noted that several sources of uncertainty may greatly affect the GREAT-ER results at temporal and spatial scales. Specifically, there is a large uncertainty associated with the EL, mainly due to the AZ DC (Table 3). However, it should be noted that uncertainty in DC and EL could be lower for medicines that have a stable consumption over time. The results suggest that the DC for antibiotics may assume dissimilar values between one municipality to another and between seasons, therefore, an optimal monitoring plan should be carefully defined to account for the DC variability in addition to the hydrological conditions. Indeed, the procedure to evaluate the DC and EL in GREAT-ER does not require measurements of AZ at the effluent, but the results of this study showed that this approach suffers from several lacks since the value of the DC at the local scale may be very dissimilar from the national value and it may vary over time being significantly correlated with the incidence of flu (Osservatorio Nazionale sull'impiego dei Medicinali, 2023). Literature reports seasonal changes in antibiotic concentrations in WWTP discharges used to treat bacterial infections (i.e. respiratory infections) (Shaheen et al., 2022). The present study confirmed changes in DC. In addition, RR may vary from one WWTP to another. These circumstances could be relevant when modelling the PEC in intermittent streams. In this work, additional sources of uncertainty that have not been quantified are the antibiotics in livestock manure, which may have been applied to agricultural fields and washed into the river. Finally, sewage overflow, which may occur during the rainy period, should be monitored and investigated, as well as the resuspension of sediments during flood events. Despite these limitations, the model application is a promising procedure that can be used at the basin scale. It can be improved based on an optimal monitoring plan developed on these preliminary results. It is evident that for antibiotics risk assessment, EL should be estimated from direct measurements of the effluent (concentration and sewage discharge).

The results showed that several reaches located downstream of the WWTPs presented a high ecotoxicological risk associated with the presence of AZ in surface waters. These results suggest that "measures" to reduce the ecotoxicological risk are needed, and innovative and sustainable technologies for removing emerging pollutants from wastewater should be developed and tested.

4.4. *Policies approaches to pharmaceutical pollutants*

At the international level, there are no legally required obligations for pharmaceutical pollutants (Miettinen and Khan, 2021). Several international agencies highlighted that the environmental risk of pharmaceuticals should be assessed quantitatively. The Organization for Economic Co-operation and Development (OECD) recognizes that current policies for managing pharmaceuticals are inadequate to protect waters and ecosystems (OECD, 2019). United Nations Environmental Program (UNEP) pointed out the need for sustainable management of chemicals since they continue to be released in large amounts into the environment (UNEP, 2019). The Word Health Organization (WHO)

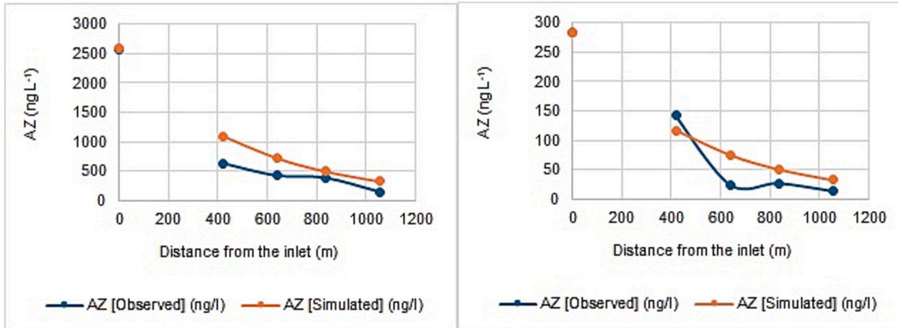

Fig. 5. Measured and modeled AZ concentration at the effluent and in surface waters downstream of the inlet in March 2021 (on the left), and in August 2021 (on the right).

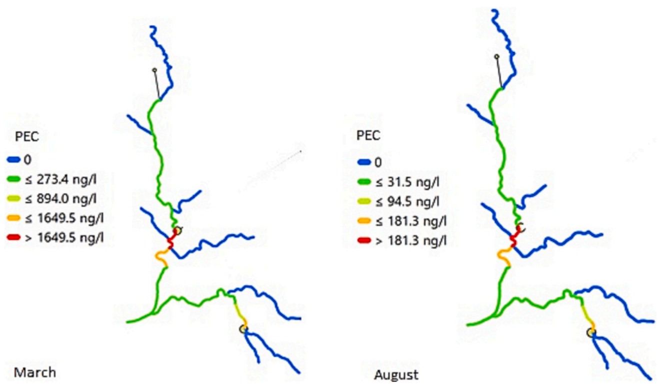

Fig. 6. Predicted Environmental Concentrations (PEC) of the AZ in the river network modeled by the GREAT-ER model in March and August.

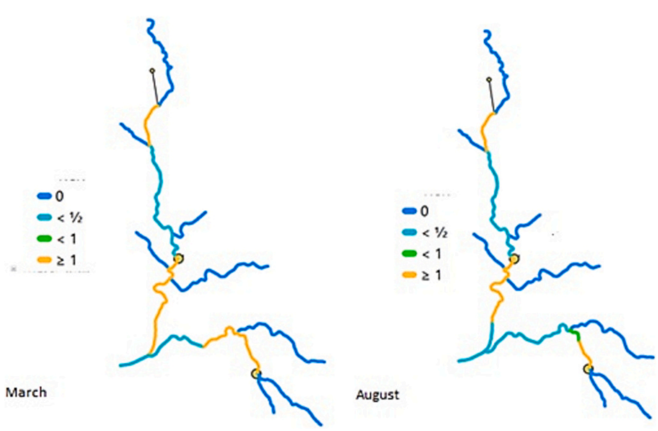

Fig. 7. Maps of the risk (PEC/PNEC) related to the presence of azithromycin in surface water in March (A) and August (B). PEC is for mean Predicted Environmental Concentrations modeled by GREAT-ER. PNEC is for the predicted no-effect concentration for azithromycin (0.019 μg l^{-1}).

highlighted the need for a comprehensive risk assessment and management in the water safety plan to prevent pharmaceuticals from entering the water supply cycle (WHO, 2012). European Commission (EC) included AZ in the 1st and 2nd Watch List (WL) under the Water Framework Directive (WFD) (Loos et al., 2018), and the observations at the EU level induced a revision of the PNEC that was fixed to a lower value (0.019 μg L^{-1}) compared to the previous threshold of the 1st WL (0.09 μg L^{-1}).

Although antibiotics are recognized as an emerging contaminant of concern, some limitations such as data availability and the lack of standardized procedure for monitoring and modelling make it difficult for risk assessment and management. This study contributed to defining a methodological approach based on monitoring and modelling for risk assessment.

5. Conclusions

The main findings of the present study indicate that the river reaches downstream of the WWTPs present a high ecotoxicological risk associated with the presence of AZ in surface waters. Measurements and modeled values of AZ concentrations showed an important in-stream attenuation of AZ concentration moving downstream of inlets. It can be concluded that in intermittent and ephemeral streams the natural streamflow (in un-impacted conditions) could be not enough to dilute the concentration of pharmaceuticals such as AZ coming from WWTPs below the environmental quality standards. These results highlight that better management of AZ consumption and innovative wastewater treatments are needed to reduce antibiotic contamination. From this perspective, this study provides the Regional Environmental Agencies with a methodological approach, which is the first step to better managing the antibiotic contamination.

It is important to highlight that some errors and a certain uncertainty degree may affect the results of this methodological approach. For instance, a few samples of AZ per year could give a picture of specific situations (i.e. malfunction of WWTP), as well as measurements taken on a single river reach could bring errors in the upscaling results at the basin scale. Indeed, the main limitations of the GREAT-ER model application are related to the input data such as DC and RR, which are affected by uncertainty. Unlike other pharmaceuticals, the DC of AZ may vary from one season to another, and the value recorded at a municipality scale may be different from national or regional values. Similarly, the RR may vary from one WWTP to another. Concerning these aspects, the take-home message of this research appears to be the need for an ad hoc monitoring plan. Monitoring should include AZ concentrations throughout the year, covering diverse hydrological and weather conditions and several reaches within a basin. In addition, AZ concentration and sewage discharge at the effluent are fundamental to correctly estimating EL.

Further studies are needed to estimate AZ concentration in sediments and the contribution from diffuse sources (i.e such as the manure spreading on fields). Investigations are also needed to assess the potential effects of sewage overflows and the ecotoxicological consequences on the river ecosystem in intermittent streams.

CRediT authorship contribution statement

A.M. De Girolamo: Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology. **G.F. Ricci:** Writing – original draft, Software, Investigation. **G. Parete:** Visualization, Software, Data curation. **O. Gómez-Navarro:** Writing – original draft, Formal analysis. **S. Pérez:** Writing – original draft, Supervision. **F. Gentile:** Writing – original draft, Resources, Funding acquisition.

Funding

This work was developed within the "Quality and management of intermittent river and groundwater in the Mediterranean basins" (INWAT) Project, supported by the European Commission and Ministry of University and Research (Italy), Program "Partnership for Research and Innovation in the Mediterranean Area" (PRIMA 2018).

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.

Data availability

Data will be made available on request.

References

Abbaspour, K.C., 2015. SWAT-CUP 2012: SWAT Calibration and Uncertainty Programs – A User Manual, 103. Eawag, Dübendorf, Switzerland.

Addis, T.Z., Adu, J.T., Kumarasamy, M., Demlie, M., 2023. Assessment of existing fate and transport models for predicting antibiotic degradation and transport in the aquatic environment: a review. Water 15, 1511. https://doi.org/10.3390/w15081511.

Aldekoa, J., Medici, C., Osorio, V., Pérez, S., Marcé, R., Barceló, D., Francés, F., 2013. Modelling the emerging pollutant diclofenac with the GREAT-ER model: application to the Llobregat River basin. J. Hazard. Mater. 263, 207–213. https://doi.org/10.1016/j.jhazmat.2013.08.057.

Almeida, A.C., Gomes, T., Antonio Baz Lomba, J., Lillicrap, A., 2021. Specific toxicity of azithromycin to the freshwater microalga Raphidocelis subcapitata. Ecotoxicol. Environ. Saf. 222, 112553. https://doi.org/10.1016/j.ecoenv.2021.112553.

Archundia, D., Boithias, L., Duwig, C., Morel, M.-C., Flores, Aviles G., Martins, J.M.F., 2018. Environmental fate and ecotoxicological risk of the antibiotic sulfamethoxazole across the Katari catchment (Bolivian Altiplano): application of the GREAT-ER model. Sci. Total Environ. 622–623 (2018), 1046–1055.

Arnold, J.G., Moriasi, D.N., Gassman, P.W., Abbaspour, K.C., White, M.J., Srinivasan, R., Santhi, C., Harme, l, R.D., Van Griesven, A., Van Liew, M.W., Kannan, N., Jha, M.K., 2012. SWAT: Model Use, Calibration, and Validation. Transactions of the ASABE 55, 1549–1559. https://doi.org/10.13031/2013.42263.

Arnold, J.G., Srinivasan, R., Muttiah, R.S., Williams, J.R., 1998. Large area hydrologic modelling and assessment—part 1: model development. J. Am. Water Resour. Assoc. 34 (1), 73–89. https://doi.org/10.1111/j.1752-1688.1998. tb05961.x.

Barra Caracciolo, A., Topp, E., Grenni, P., 2015. Pharmaceuticals in the environment: biodegradation and effects on natural microbial communities. A review. J. Pharm. Biomed. Anal. 106, 25–36.

Cappelli, F., Longoni, O., Rigato, J., Rusconi, M., Sala, A., Fochi, I., Palumbo, M.T., Polesello, S., Roscioli, C., Salerno, F., Stefani, F., Bettinetti, R., Valsecchi, S., 2022. Suspect screening of wastewaters to trace anti-COVID-19 drugs: potential adverse effects on aquatic environment. Sci. Total Environ. 824, 153756.

Cardini, A., Pellegrino, E., Ercoli, L., 2021. Predicted and measured concentration of Pharmaceuticals in Surface Water of areas with increasing anthropic pressure: a case study in the coastal area of Central Italy. Water 13, 2807. https://doi.org/10.3390/w13202807.

Carvalho, R.N., Marinov, D., Loos, R., Napierska, D., Chirico, N., Lettieri, T., 2016. Monitoring-based excercise: second review of the priority substance list under the water framework directive (final draft version). European Commission, DG Joint Research Centre Institute for Environment and Sustainability, Ispra, Italy. https://circabc.europa.eu/sd/a/7fe29322-946a-4ead-b3b9-e3b156d0c318/Monitoringbased%20Exercise%20Report_FINAL%20DRAFT_25nov2016.pdf.

Cassani, G., Matthies, M., Boeije, G., Vanrolleghem, P., Young, A., Morris, G., Gandolfi, C., Feijtel, T.C., 2001. GREAT-ER: a new tool for management and risk assessment of chemicals in river basins contribution to GREAT-ER no.10. Water Sci. Technol. 43 (2), 179–185.

Centanni, M., Ricci, G.F., De Girolamo, A.M., Gentile, F., 2024. Modeling pesticides and ecotoxicological risk assessment in an intermittent river using SWAT. Sci. Rep. 14 (6389), 1–17.

Cong, W., Stuart, B., Aihusein, N., Liu, B., Tang, Y., Wang, H., Wang, Y., Manchundiya, A., Lambert, H., 2022. Antibiotic use and bacterial infection in COVID-19 patients in the second phase of the SARS-CoV-2 pandemic: a scoping review. Antibiotics 11, 991. https://doi.org/10.3390/antibiotics11080991.

D'Ambrosio, E., De Girolamo, A.M., Spanò, M., Corbelli, V., Capasso, G., Morea, M., Velardo, R., Abdelwahab, O.M.M., Lonigro, A., Milillo, F., Ricci, G.F., Romano, G., Calabrese, A., Casale, B., Mauro, R., Pappagallo, G., Gentile, F., 2019. A spatial analysis to define data requirements for hydrological and water quality models in data-limited regions. Water 11 (2), 267. https://doi.org/10.3390/w11020267.

D'Ambrosio, E., Gentile, F., De Girolamo, A.M., 2020. Assessing the sustainability in water use at the basin scale through water footprint indicators. J. Clean. Prod. 244, 118847. https://doi.org/10.1016/j.jclepro.2019.118847.

Danner, C., Robertson, A., Behrends, V., Reiss, J., 2019. Antibiotic pollution in surface fresh waters: occurrence and effects. Sci. Total Environ. 664, 793–804. https://doi.org/10.1016/j.scitotenv.2019.01.406.

Datta, A.R., Kang, Q., Chen, B., Ye, X., 2018. Chapter four - fate and transport modelling of emerging pollutants from watersheds to oceans: a review. Adv. Mar. Biol. 81 (2018), 97–128.

De Girolamo, A.M., Drouiche, A., Ricci, G.F., Parete, G., Gentile, F., Debieche, T.-H., 2022. Characterising flow regimes in a semi-arid region with limited data availability: the nil Wadi case study (Algeria). J. Hydrol. Reg. Stud. 41, 101062. https://doi.org/10.1016/j.ejrh.2022.101062.

Di Cesare, A., Eckert, E.M., Teruggi, A., Fontaneto, D., Bertoni, R., Callieri, C., Corno, G., 2015. Constitutive presence of antibiotic resistance genes within the bacterial community of a large subalpine lake. Mol. Ecol. 24 (15). https://doi.org/10.1111/mec.13293.

Feijtel, T., Boeije, G., Matthies, M., Young, A., Morris, G., Gandolfi, C., Hansen, B., Fox, K., Holt, M., Koch, V., et al., 1997. Development of a geography-referenced regional exposure assessment tool for European rivers-GREAT-ER contribution to GREAT-ER#1. Chemosphere 34, 2351–2370.

Feitosa-Felizzola, J., Chiron, S., 2009. Occurrence and distribution of selected antibiotics in a small Mediterranean stream (Arc River, southern France). J. Hydrol. 364 (1–2), 50–57. https://doi.org/10.1016/j.jhydrol.2008.10.006.

Fox, K.K., Daniel, M., Morris, G., Holt, M.S., 2000. The use of measured boron concentration data from the GREAT-ER UK validation study (1996–1998) to generate predicted regional boron concentrations. Sci. Total Environ. 305–316.

Fukushige, M., Ngo, N.H., Lukmanto, D., Fukuda, S., Ohneda, O., 2022. Effect of the COVID-19 pandemic on antibiotic consumption: a systematic review comparing 2019 and 2020 data. Front. Public Health 10, 946077. https://doi.org/10.3389/fpubh.2022.946077.

Gagliotti, C., Banchelli, F., Buttazzi, R., Ricchizzi, E., Canziani, L.M., Rolli, M., Tacconelli, E., Moro, M.L., Berti, E., 2024. Use of azithromycin attributable to acute SARS-CoV-2 infection. Pharmacoepidemiol. Drug Saf. 33, e5857. https://doi.org/10.1002/pds.5857.

Gómez-Navarro, O., Labad, F., Manjarrés-López, D.P., Pérez, S., Montemurro, N., 2023. HRMS-targeted-DIA methodology for quantification of wastewater-borne pollutants in surface water. MethodsX, 102093. https://doi.org/10.1016/j.mex.2023.102093.

Gómez-Navarro, O., De Girolamo, A.M., Lorenz, A.W., Debieche, T.-H., Khadhar, S., Gentile, F., Chiron, S., Pérez, S., 2024. Characterization of anthropogenic impacts in Mediterranean intermittent rivers with chemical, ecological and hydrological indicators. J. Hazard. Mater. 480, 135951. https://doi.org/10.1016/j.jhazmat.2024.135951.

Grabicova, K., Grabic, R., Blaha, M., Kumar, V., Cerveny, D., Fedorova, G., Randak, T., 2014. Presence of pharmaceuticals in benthic fauna living in a small stream affected by effluent from a municipal sewage treatment plant. Water Res. 2014, 1–9.

Grandclément, C., Seyssiecq, I., Piram, A., Wong-Wah-Chung, P., Vanot, G., Tiliacos, T., Roche, N., Doumenq, P., 2017. From the conventional biological wastewater treatment to hybrid processes, the evaluation of organic micropollutant removal: a review. Water Res. 111, 297–317.

Grill, G., Khan, U., Lehner, B., Nicell, J., Ariwi, J., 2016. Risk assessment of down-the-drain chemicals at large spatial scales: model development and application to contaminants originating from urban areas in the Saint Lawrence River basin. Sci. Total Environ. 541, 825–838. https://doi.org/10.1016/j.scitotenv.2015.09.100.

Hanamoto, S., Yamamoto-Ikemoto, R., 2022. In-stream sorption of azithromycin and levofloxacin in a river receiving sewage treatment plant effluent. Environ. Pollut. 307, 119568.

Hanamoto, S., Nakada, N., Jürgens, M.D., et al., 2018. The different fate of antibiotics in the Thames River, UK, and the Katsura River, Japan. Environ. Sci. Pollut. Res. 25, 1903–1913. https://doi.org/10.1007/s11356-017-0523-z.

Hao, X., Cao, Y., Zhang, L., Zhang, Y., Liu, J., 2015. Fluoroquinolones in the Wenyu River catchment, China: occurrence simulation and risk assessment: exposure simulation and risk assessment of fluoroquinolones. Environ. Toxicol. Chem. 34, 2764–2770. https://doi.org/10.1002/etc.3158.

Hargreaves, G.H., 1975. Moisture availability and crop production. Trans. ASAE 18 (5), 980–984. https://doi.org/10.13031/2013.36722.

Holt, M., Fox, K., Daniel, M., Buckland, H., 2003. Linear alkylbenzene sulfonate and boron monitoring in four catchments in the UK contribution to GREAT-ER #11. Sci. Total Environ. 314–316, 271–288. https://doi.org/10.1016/S0048-9697(03)00107-4.

Jagiello, K., Mostrag-Szlichtyng, A., Gajewicz, A., Kawai, T., Imaizumi, Y., Sakurai, T., Yamamoto, H., Tatarazako, N., Mizukawa, K., Aoki, Y., Suzuki, N., Watanabe, H., Puzyn, T., 2015. Towards modelling of the environmental fate of pharmaceuticals using the QSPR-MM scheme. Environ. Model Softw. 72, 147–154. https://doi.org/10.1016/j.envsoft.2015.06.013.

Kehrein, N., Berlekamp, J., Klasmeier, J., 2015. Modelling the fate of down-the-drain chemicals in whole watersheds: new version of the GREAT-ER software. Environ. Model Softw. 64, 1–8. https://doi.org/10.1016/j.envsoft.2014.10.018.

Keller, V., 2006. Risk assessment of "down-the-drain" chemicals: search for a suitable model. Sci. Total Environ. 360, 305–318. https://doi.org/10.1016/j.scitotenv.2005.08.042.

Labad, F., Ginebreda, A., Criollo, R., Vázquez-Suñé, E., Pérez, S., Jurado, A., 2023. Occurrence, data-based modelling, and risk assessment of emerging contaminants in an alluvial aquifer polluted by river recharge. Environ. Pollut. 316 (part 1), 120504. https://doi.org/10.1016/j.envpol.2022.120504.

Lämmchen, V., Niebaum, G., Berlekamp, J., Klasmeier, J., 2021. Georeferenced simulation of pharmaceuticals in whole watersheds: application of GREAT-ER 4.1 in Germany. Environ. Sci. Pollut. Res. Int. 28, 21926. https://doi.org/10.1007/s11356-020-12189-7.

Leone, M., Gentile, F., Lo Porto, A., Ricci, G.F., Schürz, C., Strauch, M., Volk, M., De Girolamo, A.M., 2024. Setting an environmental flow regime under climate change in a data-limited Mediterranean basin with temporary river. J. Hydrol. Reg. Stud. 52, 101698.

Loos, R., Marinov, D., Sanseverino, I., Napierska, D., Lettieri, T., 2018. Review of the 1st Watch List Under the Water Framework Directive and Recommendations for the 2nd Watch List, EUR 29173 EN. Publications Office of the European Union, Luxembourg. https://doi.org/10.2760/614367. https://op.europa.eu/en/publication-detail/-/publication/fd59ef1f-78ea-11e8-ac6a-01aa75ed71a1/language-en (18/02/2025).

Lucas-Borja, M.E., Carrà, B.G., Nunes, J.P., Bernard-Jannin, L., Zema, D.A., Zimbone, S. M., 2020. Impacts of land-use and climate changes on surface runoff in a tropical forest watershed (Brazil). Hydrol. Sci. J. 65 (11). https://doi.org/10.1080/02626667.2020.1787417.

Mandaric, L., Kalogianni, E., Skoulikidis, N., Petrovic, M., Sabater, S., 2019. Contamination patterns and attenuation of pharmaceuticals in a temporary Mediterranean river. Sci. Total Environ. 647. https://doi.org/10.1016/j.scitotenv.2018.07.308.

Mheidli, N., Malli, A., Mansour, F., Al-Hindi, M., 2022. Occurrence and risk assessment of pharmaceuticals in surface waters of the Middle East and North Africa: a review. Sci. Total Environ. 851, 158302.

Miettinen, M., Khan, S.A., 2021. Pharmaceutical pollution: a weakly regulated global environmental risk. Rev. Eur. Comp. Int. Environ. Law 31 (1), 75–88. https://doi.org/10.1111/reel.12422.

Mirzaie, F., Teymori, F., Shahcheragh, S., Dobaradaran, S., Arfaeinia, H., Kafaei, R., Sahebi, S., Farjadfard, S., Ramavandi, B., 2022. Occurrence and distribution of azithromycin in wastewater treatment plants, seawater, and sediments of the northern part of the Persian Gulf around Bushehr port: a comparison with pre-COVID 19 pandemic. Chemosphere 307 (Pt 4), 135996. https://doi.org/10.1016/j.chemosphere.2022.135996.

Mohamad, I.-N., Wong, C.K.W., Chew, C.C., Leong, E.L., Lee, B.H., Moh, C.K., Chenasammy, K., Lim, S.C.-L., Ker, H.B., 2022. The landscape of antibiotic usage among COVID-19 patients in the early phase of pandemic: a Malaysian national perspective. J. Pharmaceut. Policy Pract. 15, 4. https://doi.org/10.1186/s40545-022-00404-4.

Morales-Paredes, C.A., Rodrìguez-Dìaz, J.M., Boluda-Botella, N., 2022. Pharmaceutical compounds used in the COVID-19 pandemic: a review of their presence in water and treatment techniques for their elimination. Sci. Total Environ. 814 (2022), 152691. https://doi.org/10.1016/j.scitotenv.2021.152691.

Moriasi, D.N., Arnold, J.G., Van Liew, M.W., Bingner, R.L., Harmel, R.D., Veith, T.L., 2007. Model evaluation guidelines for systematic quantification of accuracy in watershed simulations. Trans. ASABE 50, 885–900.

National Center for Biotechnology Information, 2023. PubChem Compound Summary for CID 447043, Azithromycin. Retrieved November 24, 2023 from. https://pubchem.ncbi.nlm.nih.gov/compound/Azithromycin.

OECD, 2019. Pharmaceutical Residues in Freshwater: Hazards and Policy Responses, OECD Studies on Water. OECD Publishing, Paris.

Osorio, V., Proia, L., Ricart, M., Pérez, S., Ginebreda, A., Cortina, J.L., Sabater, S., Barceló, D., 2014. Hydrological variation modulates pharmaceutical levels and biofilm responses in a Mediterranean river. Sci. Total Environ. 472, 1052–1061.

Osservatorio Nazionale sull''impiego dei Medicinali, 2023. L'uso degli antibiotici in Italia. Rapporto Nazionale 2021. Roma: Agenzia Italiana del Farmaco, 2023. The Medicines Utilisation Monitoring Centre. National Report on antibiotics use in Italy. Year 2021. Italian Medicines Agency, Rome.

Palma, P., Fialho, S., Lima, A., Novais, M.H., Costa, M.J., Montemurro, N., Pérez, S., Lopez de Alda, M., 2020. Pharmaceuticals in a Mediterranean Basin: the influence of temporal and hydrological patterns in environmental risk assessment. Sci. Total Environ. 709 (1), 136205. https://doi.org/10.1016/j.scitotenv.2019.136205.

Pan, M., Yau, P.C., 2021. Fate of Macrolide Antibiotics with Different Wastewater Treatment Technologies. Water Air Soil Pollut 232, 103. https://doi.org/10.1007/s11270-021-05053-y.

Patel, M., Kumar, R., Kishor, K., Pittman, C.U., Mohan, D., 2019. Pharmaceuticals of Emerging Concern in aquatic systems: chemistry, occurrence, effects, and removal methods. Chem. Rev. 119, 3510–3673. https://doi.org/10.1021/acs.chemrev.8b00299.

Reoyo-Prats, B., Aubert, D., Sellier, A., Roig, B., Palacios, C., 2018. Dynamics and sources of pharmaceutically active compounds in a coastal Mediterranean river during heavy rains. Environ. Sci. Pollut. Res. 25 (7), 6107–6121.

Ricci, G.F., Zahi, F., D'Ambrosio, E., De Girolamo, A.M., Parete, G., Debieche, T.-H., Gentile, F., 2022. Evaluating flow regime alterations due to point sources in intermittent rivers: a modelling approach. Journal of. Agric. Eng. 53 (2). https://doi.org/10.4081/jae.2022.1333.

Ricci, G.F., Centanni, M., De Girolamo, A.M., Gentile, F., 2023. Modelling daily streamflow in a temporary karst river system: comparing three approaches using the SWAT model. Hydrol. Sci. J. 68 (3), 462–473. https://doi.org/10.1080/02626667.2023.2174027.

Rodriguez-Mozaz, S., Vaz-Moreira, I., Varela Della Giustina, S., Llorca, M., Barceló, D., Schubert, S., Berendonk, T.U., Michael-Kordatou, I., Fatta-Kassinos, D., Martinez, J. L., Elpers, C., Henriques, I., Jaeger, T., Schwartz, T., Paulshus, E., O'Sullivan, K., Pärnänen, K.M.M., Virta, M., Do, T.T., Walsh, F., Manaia, C.M., 2020. Antibiotic residues in final effluents of European wastewater treatment plants and their impact on the aquatic environment. Environ. Int. 140, 105733. https://doi.org/10.1016/j.envint.2020.105733.

Sanseverino, I., Navarro Cuenca, A., Loos, R., Marinov, D., Lettieri, T., 2018. State of the Art on the Contribution of Water to Antimicrobial Resistance, EUR 29592 EN. Publications Office of the European Union, Luxembourg. https://doi.org/10.2760/771124.

Schowanek, D., Webb, S., 2002. Exposure simulation for pharmaceuticals in European surface waters with GREAT-ER. Toxicol. Lett. 131, 39–50.

Schowanek, D., Fox, K., Holt, M., Schroeder, F.R., Koch, V., Cassani, G., Matthies, M., Boeije, G., Vanrolleghem, P., Young, A., Morris, G., Gandolfi, C., Feijtel, T.C., 2001. GREAT-ER: a new tool for management and risk assessment of chemicals in river basins. Contribution to GREAT-ER #10. Water Sci. Technol. 43 (2), 179–185 (PMID: 11380178).

Schulze, C., Matthies, M., 2001. Georeferenced aquatic fate simulation of cleaning agent and detergent ingredients in the river Rur catchment (Germany). Sci. Total Environ. 280, 55–77.

Shaheen, J.F., Sizirici, B., Yildiz, I., 2022. Fate, transport, and risk assessment of widely prescribed pharmaceuticals in terrestrial and aquatic systems: a review. Emerg. Contamin. 8, 216–228. https://doi.org/10.1016/j.emcon.2022.04.001.

Stamatis, N., Triantafyllidis, V., Hela, D., Konstantinou, I., 2013. Occurrence and distribution of selected pharmaceutical compounds on sewage-impacted section of river Acheloos, Western Greece. Int. J. Environ. Anal. Chem. 93 (15), 1602–1619.

Tran, N.H., Chen, H., Reinhard, M., Mao, F., Gin, K.Y.-H., 2016. Occurrence and removal of multiple classes of antibiotics and antimicrobial agents in biological wastewater treatment processes. Water Res. 104, 461–472.

UNEP, 2019. Global Chemicals Outlook II: From Legacies to Innovative Solutions: Implementing the 2030 Agenda for Sustainable Development. Synthesis Report. United Nation Environmental Program, p. 102. https://www.unep.org/resources/report/global-chemicals-outlook-ii-legacies-innovative-solutions (access 2nd March 2023).

United States Department of Agriculture–Soil Conservation Service (USDA-SCS), 1972. National Engineering Hand-Book, Section 4, Hydrology. USDA Soil Conservation Service, Washington, DC.

US-EPA, 2009. Health Care Industry Unused Pharmaceuticals Detailed Study 2007–2009 Data Collection and Outreach. Public Docket for the Preliminary 2010 Effluent Guidelines Program Plan EPA Docket Number EPA-HQ-OW-2008-0517. www.regulations.gov. https://www.epa.gov/sites/default/files/2015-11/documents/health-care-unused-pharms_detailed-study_2009.pdf (access 28/02/2023).

van Leeuwen, C.J., Vermeire, T.G., 2007. Risk Assessment of Chemicals: An Introduction, 2 ed. Springer, Dordrecht. https://doi.org/10.1007/978-1-4020-6102-8.

Verlicchi, P., Al Aukidy, M., Zambello, M., 2012. Occurrence of pharmaceutical compounds in urban wastewater: removal, mass load and environmental risk after a secondary treatment - a review. Sci. Total Environ. 429, 123–155.

Vermillion Maier, M.L., Tjeerdema, R.S., 2018. Azithromycin sorption and biodegradation in a simulated California river system. Chemosphere 190, 471–480. https://doi.org/10.1016/j.chemosphere.2017.10.008.

von Schiller, D., Bernal, S., Dahm, C.N., Martí, E., 2017. Nutrient and Organic Matter Dynamics in Intermittent Rivers and Ephemeral Streams Chapter 3.2 - Intermittent Rivers and Ephemeral Streams Ecology and Management, pp. 135–160. https://doi.org/10.1016/B978-0-12-803835-2.00006-1.

WHO, 2012. Pharmaceuticals in Drinking-Water. WHO Library Cataloguing-in-Publication Data. Word Health Organization, Geneva, Switzerland.

WHO, 2025. Defined Daily Dose: Definition and General Considerations. https://www.who.int/tools/atc-ddd-toolkit/about-ddd (Access 21 Feb 2025).

Wilkinson, et al., 2022. Pharmaceutical pollution of the world's rivers. PNAS 119 (8), e2113947119. https://doi.org/10.1073/pnas.2113947119.

Wise-Freshwater, 2024. WISE - Freshwater Information System for freshwater Europe. https://water.europa.eu/freshwater/europe-freshwater/water-framework-directive/ecological-status-of-surface-water#:~:text=In%20Europe%20EU%2D27to%20meet%20good%20ecological%20status (access 17/02/2025).

Zhang, L., Cao, Y., Hao, X., Zhang, Y., Liu, J., 2015. Application of the GREAT-ER model for environmental risk assessment of nonylphenol and nonylphenol ethoxylates in China. Environ. Sci. Pollut. Res. 22, 18531–18540. https://doi.org/10.1007/s11356-015-5352-3.