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Antibiotics in the Basque coast (N Spain): Occurrence in waste and receiving waters, and risk assessment (2017–2020)

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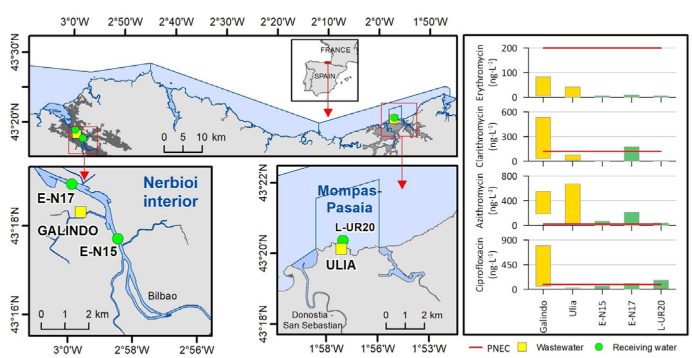
HIGHLIGHTS

- Macrolide antibiotics showed frequency of occurrence (F (%)) above 65 %.
- Concentrations of antibiotics showed a generalized decrease from 2017 to 2020.
- The studied antibiotics, except erythromycin, may pose a risk to the environment.
- Emphasise the importance of continuous monitoring for a better assessment

GRAPHICAL ABSTRACT



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ABSTRACT

The study of the presence of antibiotics in the aquatic environment is a preliminary step to analyse their possible harmful effects on aquatic ecosystems. In order to monitor their occurrence in the aquatic environment, the European Commission established in 2015, 2018, and 2020 three Watch Lists of substances for Union-wide monitoring (Decisions (EU) 2015/495, 2018/840, and 2020/1161), where some antibiotics within the classes of macrolides, fluoroquinolones and penicillins were included.

In the Basque coast, northern Spain, three macrolide antibiotics (erythromycin, clarithromycin, azithromycin) and ciprofloxacin were monitored quarterly from 2017 to 2020 (covering a period before and after the COVID19 outbreak), in water samples collected from two Waste Water Treatment Plants (WWTPs), and three control points associated with receiving waters (transitional and coastal water bodies). This work was undertaken for the Basque Water Agency (URA).

The three macrolide antibiotics in water showed a frequency of quantification >65 % in the Basque coast, with higher concentrations in the WWTP emission stations than in receiving waters. Their frequency of quantification decreased from 2017 to 2020, as did the consumption of antibiotics in Spanish primary care since 2015. Ciprofloxacin showed higher frequencies of quantification in receiving waters than in wastewaters, but the highest concentrations were observed in the WWTP emission stations. Although consumption of fluoroquinolones (among which is ciprofloxacin) in primary care in the Basque Country has decreased in recent years, this trend was not observed in the waters sampled in the present study. On the other hand, concentrations of clarithromycin, azithromycin, and ciprofloxacin in receiving waters exceeded their respective Predicted No-Effect Concentrations, so they could pose an environmental risk.

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These substances are widely used in human and animal medicine, so, although only ciprofloxacin is included in the third Watch List, it would be advisable to continue monitoring macrolides in the Basque coast as well.

1. Introduction

Antibiotics are a group of pharmaceuticals widely used in both human and veterinary medicine since the 1950s (Carvalho and Santos, 2016; Felis et al., 2020; Szymańska et al., 2019). Their excessive and inappropriate use, among other factors, has led to the development and rapid expansion of bacteria that become antibiotic-resistant (Davies and Davies, 2010). As a result, antibiotics could become ineffective and infections harder to treat, increasing the risk to environment and human health (Carvalho and Santos, 2016; O'Flynn et al., 2021; Osorio et al., 2016; WHO, 2015; Wu et al., 2022; Zheng et al., 2021).

In Europe, several projects, actions, and initiatives have been promoted to investigate antibiotic consumption and research on environmental contamination to mitigate antimicrobial resistance (Carvalho and Santos, 2016). Based on the information provided by the European Centre for Disease Prevention and Control (ECDC) and the European Surveillance of Veterinary Antimicrobial consumption (ESVAC), antibiotic consumption in Europe has shown a decrease in the last years (ECDC, 2021; ESVAC, 2021), as did in Spain (PRAN; https://www.resistenciaantibioticos.es/es, last access 31 Jan 2022).

Since antibiotics are poorly metabolized in humans and animals after their consumption, they are excreted in urine and faeces, entering the environment through wastewater and manure (Beiras, 2021; Carvalho and Santos, 2016; Langbehn et al., 2021; Polianciuc et al., 2020; Qiao et al., 2018). The occurrence of antibiotics in the water environment may cause serious problems to aquatic organisms at different trophic levels, including both immediate effects (acute toxicity) and long-term effects (chronic toxicity) (Anh et al., 2021; Carvalho and Santos, 2016; Felis et al., 2020). Furthermore, as they are also used in veterinary medicine, they can cause problems in terrestrial ecosystems, such as nitrification of bacteria, and reach the aquatic environment through run-off. They are also toxic to six of the bacteria used in the processes of some biological treatments in Waste Water Treatment Plants (WWTPs), and can thus alter the processes or treatments of these utilities (Santos et al., 2010).

Although the use and sales of antibiotics have been regulated in recent years, e.g., in Europe (EU Regulation 2019/6; EC, 2019) and Spain (Royal Legislative Decree 1/2015; BOE, 2015), these substances are increasingly appearing in environmental studies (Szymańska et al., 2019; Zheng et al., 2021). As contaminants of emerging concern, monitoring their presence in the aquatic environment has been regarded as important in some legislation (e.g., the Water Framework Directive -WFD-; Directive 2000/60/EC; EC, 2000). In fact, due to the threats that the occurrence of antibiotics could cause in the environment, and the limited knowledge about the risk they could pose to humans and living organisms (Carvalho et al., 2015; Carvalho et al., 2016; Felis et al., 2020; Loos et al., 2018), the European Commission included three macrolides (erythromycin, azithromycin and clarithromycin) in the first and second Watch Lists (EC, 2015, 2018), and ciprofloxacin and amoxicillin in the second and third ones (EC, 2018, 2020). Since the duration of a continuous Watch List monitoring period for any individual substance shall not exceed four years, macrolide antibiotics were removed from the third Watch List (EC, 2020). If hazards of any of these substances are recognized, they can be promoted to priority substances and the corresponding environmental quality standards (EQS) will be determined (O'Flynn et al., 2021).

The inclusion of antibiotics in the Watch List is consistent with the European "One Health Action Plan to combat Antimicrobial Resistance", which supports the use of the Watch List to improve knowledge of antimicrobials in the environment (EC, 2017). This plan encourages the implementation of national plans by European Member States, including Spain, whose National Plan against Antimicrobial Resistance (PRAN; https://www.resistenciaantibioticos.es/es, last access 31 Jan 2022) was approved in 2014.

Although the implementation of these plans and programmes may lead to a decrease in antibiotic consumption, most countries do not have yet appropriate legislation or monitoring programmes for their routinely analysis and assessment (Sousa et al., 2019) to support such a decreasing trend in the environment, and to take informed decisions on management measures. Recently, different studies that include the occurrence and risk of the considered antibiotics have been published worldwide (e.g., Anh et al., 2021; Barbosa et al., 2016; Fu et al., 2022; Lu et al., 2022; Lyu et al., 2020; Rodriguez-Mozaz et al., 2020; Wu et al., 2021; Wu et al., 2022; Zheng et al., 2021). In the case of the Basque Country (Northern Spain; Fig. 1), the Basque Water Agency (URA) has a long record of monitoring estuarine and coastal waters for chemical status assessment (Menchaca et al., 2014; Solaun et al., 2013; Tueros et al., 2009), and since 2016 Watch List substances have been included in the monitoring (Solaun et al., 2021). The Basque coast is a densely populated area, especially around the cities of San Sebastián and Bilbao, and with a long industrial history, which contributed to estuarine and coastal contamination and degradation in the past (Borja et al., 2016). The monitoring carried out to implement the WFD has shown that this region has substantially recovered from industrial pollution (Borja et al., 2016). Similarly, it could be useful in determining the occurrence and risk of antibiotics in the area, and to prioritize substances to be monitored in the future (Solaun et al., 2021).

In this context, the main objectives of this research were to investigate the occurrence and spatial-temporal variation of the Watch List antibiotics, following European legislative decisions, in the estuarine and coastal waters of the Basque Country, and to assess their potential environmental risk. Since the local conditions investigated can be representative of similar scenarios, in the near future data obtained in this study could be useful to take management decisions regarding monitoring of emerging contaminants such as antibiotics in aquatic environments, as required by the WFD.

2. Materials and methods

2.1. Study area and sample collection

The study was carried out in the Basque coast, in the southeast of the Bay of Biscay. Focused on two highly coastal populated areas close to the cities of Bilbao and San Sebastian (Fig. 1), the associated WWTPs were selected: (i) Galindo, which serves Bilbao city and all towns around the Ibaizabal-Nerbioi estuary, an urban agglomeration (Gran Bilbao) of 1.2 million population equivalents, and with its discharge point located in the Nerbioi interior transitional water body; and (ii) Loiola -discharge point located in Ulia, in the Mompas-Pasaia coastal water body-, serving the Donostia-San Sebastián urban agglomeration of 0.55 million population equivalents. The receiving waters corresponding to these emission points are routinely monitored for the ecological and chemical status assessment by URA (Borja et al., 2021).

The Watch List antibiotics were analysed in both WWTPs (emission sampling points: Galindo, and Ulia) and in three sampling stations related to the receiving waters of their discharges (E-N15, E-N17 and L-UR20) (Fig. 1 and Table S1, in Supplementary material, for details).

Water samples were collected quarterly (spring, summer, autumn, winter) from May 2017 to November 2020. Grab water samples were collected at the outlet of the WWTPs, and in receiving water bodies. Surface waters were collected using 5 L Niskin bottles, at low tide for the estuarine

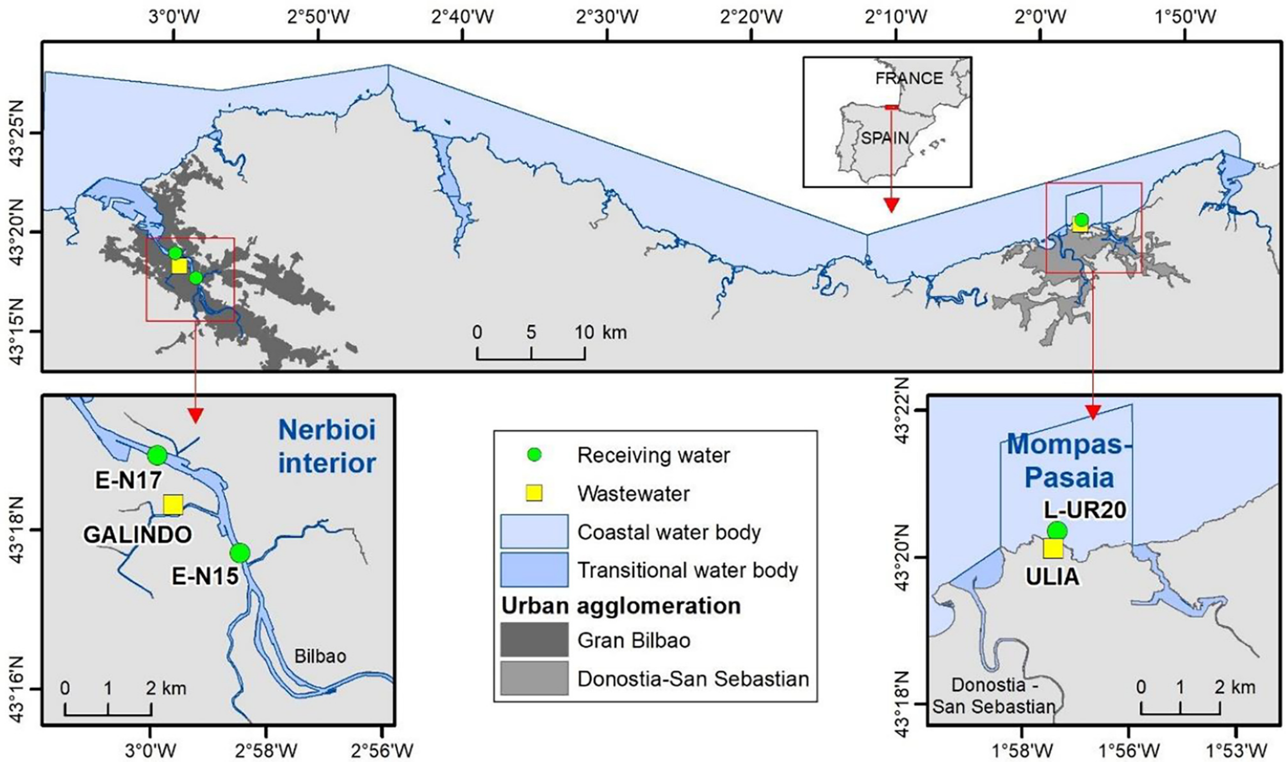

Fig. 1. Sampling stations in the study area. In yellow, sampling points related to wastewater (Galindo and Ulia), and in green, sampling points in receiving waters (E-N15, E-N17 and L-UR20). The areas of Greater Bilbao and Donostia-San Sebastian are indicated, which include other nearby localities whose waters are collected by the WWTPs sampled in this study.

locations (E-N17 and E-N15) and independent of the tide level at the coastal location (L-UR20). Once in the laboratory, in preparation for the analysis of the Watch List antibiotics, the water samples were allowed to settle for a few minutes at room temperature, then a 500 mL-aliquot was transferred to a volumetric flask containing a mixture of surrogate compounds (see Section 2.2), subsequently filtrated through 0.7 μm glass fiber filters and stored in amber polyethylene terephthalate (PET) bottles at −20 °C.

2.2. Chemicals and reagents

Four antibiotics were analysed in the water samples from the Basque coast. Macrolide antibiotics (erythromycin, clarithromycin and azithromycin) were included in the first and second Watch Lists, but not in the third one. Ciprofloxacin, however, was included in the second Watch List and has been also considered in the third Watch List (Table 1). Amoxicillin, also included in the second and third watch lists, was initially included within the group of target analytes, but it was finally disregarded due to poor method performance.

Analytical standards of these substances and isotopically labelled analogues used as surrogate standards (SS) in the quantification process were provided by Sigma Aldrich (Madrid, Spain) and Toronto Research Chemicals (North York, Canada). Individual stock solutions were prepared in methanol at a concentration of 1 mg·mL^{-1}. These solutions were used to prepare working standard mixtures at different concentrations by appropriate dilution in methanol. These standard mixtures were then used to freshly prepare the aqueous calibration solutions containing the target compounds and the isotopically labelled compounds. A methanolic solution containing only the isotopically labelled standards was also prepared to fortify the water samples immediately after collection. All standard solutions were stored in the dark at −20 °C until use.

All solvents used (HPLC-grade) as well as formic acid (> 98 %) were supplied by Merck (Darmstadt, Germany).

Table 1
Antibiotics included in the Watch Lists, their Chemical Abstract Service (CAS) number, maximum acceptable method detection limits (MDL) established by the European Commission (EC, 2015, 2018, 2020), and the analytical method detection (MDL) and quantification limits (MQL) in the present study. Predicted No-Effect Concentration (PNEC), according to Loos et al. (2018).

Substance	CAS number	Maximum acceptable MDL (ng·L^{-1})			MDL	MQL	PNEC
		EC (2015)	EC (2018)	EC (2020)	(ng·L^{-1})	(ng·L^{-1})	(ng·L^{-1})
Erythromycin	114-07-8	90	19	–	0.024–0.035	0.08–5.0	200[a]
Clarithromycin	81103-11-9	90	19	–	0.05	0.17–2.5	120[b]
Azithromycin	83905-01-5	90	19	–	0.05	0.17–15	19[b]
Amoxicillin	26787-78-0	–	78	78	n/a	n/a	78[c]
Ciprofloxacin	85721-33-1	–	89	89	0.5	1–1.67	89[b]

n/a: not analysed.
PNEC taken from.
[a] Carvalho et al., 2015.
[b] Oekotoxzentrum, Eawag/EPFL (CH). Proposals for Acute and Chronic Quality Standards https://www.ecotoxcentre.ch/expert-service/quality-standards/proposals-for-acute-and-chronic-quality-standards/.
[c] Loos et al., 2018.

Whatman® glass fiber filters (GF/F, 0.7 μm pore size) were supplied by Merck (Barcelona, Spain). On-line solid-phase extraction cartridges CHROspe PLRP-s (styrene/divinylbenzene polymer, 10 mm × 2 mm i.d., 15–20 μm particle size) were purchased at Spark Holland (Emmen, The Netherlands) (currently available at Axel Semrau GmbH & Co. KG, Srockhövel, Germany).

2.3. Analysis of antibiotics

The analytical methods had to be developed and implemented to comply with the requirements for the intended analytical applications, including the sensitivity requirements set in the European decisions (EC, 2015, 2018, 2020).

The antibiotics were analysed with a method based on isotope dilution on-line solid-phase extraction – liquid chromatography – tandem mass spectrometry (SPE-LC-MS/MS) using a Prospekt-2 automated extraction system (Spark Holland, Emmen, The Netherlands) coupled on-line with a 1525 binary HPLC pump (Waters, Milford, MA, USA) and a triple quadrupole mass spectrometer Xevo TQ (Waters) (Solaun et al., 2021). Preconcentration of the samples, previously diluted with HPLC-grade water 1:1 (*v*/v), was performed by passing 30 mL of the diluted solution through polymeric PLRP-s cartridges. Chromatographic separation was achieved with a Purospher STAR RP-18 column (100 mm × 2 mm, 5 μm, from Merck, Darmstadt, Germany) and a mobile phase consisting of water and acetonitrile, both modified with 0.1 % formic acid to enhance ionization and chromatographic separation. MS/MS detection was carried in the positive electrospray mode (ESI+) acquiring two selected reaction monitoring (SRM) transitions per target analyte and one per SS (Table S2, in Supplementary material). Quantification according to the isotope dilution method allowed to correct variable matrix effects and confirm suitable instrument performance. Method detection limits (MDLs) achieved were lower than the maximum acceptable MDLs (Table 1) set in the regulation. Amoxicillin, initially included within the group of target analytes was finally disregarded due to poor method performance. Quality controls, i.e., an aqueous standard solution containing the compounds and corresponding surrogate standards at concentrations of 50 ng·L^{-1} and 5 ng·L^{-1}, respectively, were analysed every 6 samples to check the correct operation of the instrument. Solvent blanks (HPLC-grade water) injected every 3 samples to check for potential analyte carryover between injections did not show presence of the target analytes. MS signals observed for the quinolones in the method blanks (HPLC-grade water processed following the same treatment protocol as samples and hence fortified with the surrogate standard mixture), likely coming from their presence as impurities in the purchased SS, were taken into account (subtracted) at the time of sample quantification.

2.4. Data analysis

Taking into account that concentrations below MDL (corresponding to 27 % of the measured concentrations) are considered as not quantifiable by water managers, in all statistical analysis, non-detected compounds (<MDL) were considered as below the method quantification limit (<MQL). Hence, in accordance with the Commission Directive 2009/90/EC (EC, 2009), chemical concentrations <MQL were set to half of the value of the limit of quantification concerned (i.e., MQL/2) for the calculation of mean values. Since quantification limits changed throughout the studied period, as they depend on the status of the analytical instrumentation and the samples themselves, where a calculated mean value was below the maximum MQL, the value was referred to as the maximum MQL.

Compound ubiquity was assessed through the calculation of the frequency of quantification (F (%)), which corresponds to the percentage of cases above the MQL compared to the total number of cases analysed:

$$F(\%) = \frac{n^{\circ}\ of\ samples > MQL}{n^{\circ}\ of\ analysed\ samples} \times 100$$

Since there are no EQS defined for the studied antibiotics, some authors propose to use risk quotients (RQ) for assessing the intensity of local impacts (Sousa et al., 2018; von der Ohe et al., 2011). To estimate the impact of these antibiotics on the receiving water bodies, the RQ of each measured concentration in each sample was determined as the ratio of the measured concentration (MC) to the predicted no-effect concentration (PNEC) values (Table 1), according to the European technical guidance document on risk assessment (EC, 2003):

$$RQ = \frac{MC}{PNEC}$$

Regarded as a concentration below which unacceptable effects on organisms will most likely not occur, the PNEC can be derived using an assessment factor approach or, when sufficient data is available, using statistical extrapolation methods (EC, 2003). The PNEC values used in the present study were initially calculated by Carvalho et al. (2015) and have been recently updated by Loos et al. (2018) (Table 1).

The RQs are classified into three risk levels: (i) RQ < 0.1 indicate a low risk; (ii) 0.1 ≤ RQ ≤ 1 indicate a medium risk; and (iii) RQ > 1 reveal a high risk (Gusmaroli et al., 2019; Sousa et al., 2018). In this study, the risk was considered as low for compounds present at concentrations <MQL.

The RQ approach described above characterises toxicity according to measured concentrations but ignores the possibility that aquatic organisms can be exposed to potentially dangerous levels. Certain substances are present in water in the long term and have a greater impact than pollutants present in the short term, so the risk of substances that are frequently quantified and those that are occasionally quantified should be different. Therefore, the optimised risk ratio (RQ_f), based on the mean RQ value and the frequency of concentrations above the PNEC (F_{PNEC}), was also considered (Zhou et al., 2019).

$$RQ_f = RQ_{mean} \cdot F_{PNEC} = \frac{Mean\ concentration}{PNEC} \cdot \frac{n^{\circ}\ of\ samples\ above\ PNEC}{n^{\circ}\ of\ samples\ determined}$$

The RQ_f is classified into five levels: (i) if $RQ_f \geq 1$, high environmental risk is expected (high); (ii) if $1 > RQ_f \geq 0.1$, moderate environmental risk is expected (moderate); (iii) if $0.1 > RQ_f \geq 0.01$, small-scale adverse effect is expected (endurable); (iv) if $0.01 > RQ_f > 0$, the effect is quite limited (negligible); and (v) if $RQ_f = 0$, no risk is expected (safe) (Zhou et al., 2019).

In general, it should be noted that most toxicity studies for risk assessment are done for individual compounds, but substances do not appear alone in the environment. Several studies have shown that concentrations of these families, and in particular drugs, have cumulative effects, so that individual concentrations of substances are lower than expected to cause effects, but the mixed presence of these substances in the environment can cause toxic effects (Branchet et al., 2021; DeLorenzo and Fleming, 2008; Santos et al., 2010), although much remains to be studied in this area.

3. Results and discussion

3.1. Occurrence of antibiotics in the study area

Globally, the considered macrolide antibiotics (erythromycin, clarithromycin and azithromycin) showed frequency of occurrence (F (%)) above 65 % in the Basque coast waters, for the period 2017–2020 (Table S3, in Supplementary material), suggesting a widespread occurrence of these antibiotics. Higher frequencies were observed for clarithromycin in wastewater (97 %) than in receiving waters (73 %), and similar ones for erythromycin (67 % and 64 %, respectively) and azithromycin (73 % and 76 %, respectively). Samples collected in the Cádiz Bay in summer 2015 also showed frequencies of detection higher than 64 % for these macrolide antibiotics (Biel-Maeso et al., 2018); these substances were present even in wastewater and sea water sampled in the Antarctic Peninsula region (Hernández et al., 2019).

Concerning ciprofloxacin, it was quantified in 48 % of the samples taken from 2017 to 2020. For this substance higher frequencies of occurrence were observed in receiving waters (52 %) than in wastewater (43 %),

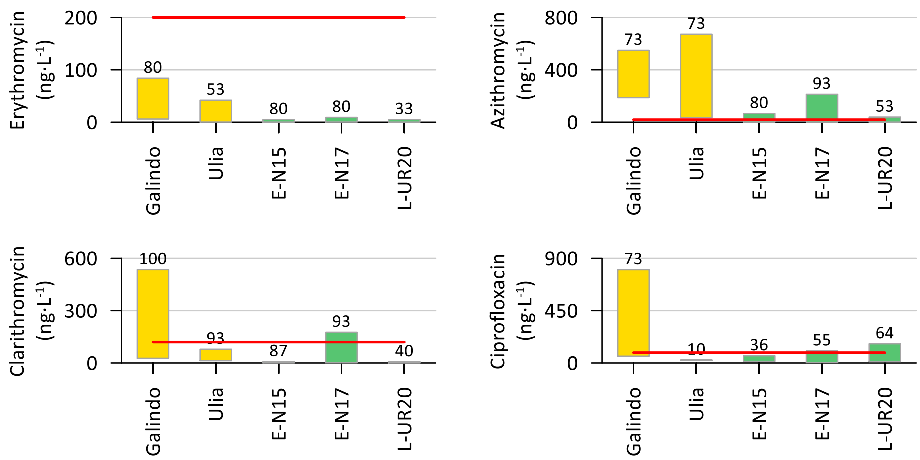

Fig. 2. Range of concentrations (ng·L^{-1}) of antibiotics quantified in the Basque coast, by sampling station (in yellow, wastewaters; in green, receiving waters). The numbers represent frequencies of quantification (%).

being a diffuse source from animal farms in the study area a possible origin of this substance. Mijangos et al. (2018), however, observed frequencies of detection higher than 80 % in three Basque WWTPs (Galindo, Gorliz and Gernika) studied between February 2016 and February 2017, and frequencies lower than 45 % in receiving waters.

3.2. Spatial distribution of antibiotics

Total concentrations of the considered antibiotics ranged from not quantified to 1323 ng·L^{-1} in the Basque coast for the period 2017–2020 (Fig. S1, in Supplementary material). Similar maximum values were observed in a previous study carried out in Cadiz (SW Spain; 1195 ng·L^{-1}; Biel-Maeso et al., 2018).

Pharmaceutical contamination in the marine environment could vary due to spatial factors such as pollution sources, the marine site configuration (coast, bay, estuary, etc.), or depth and width of the site (Branchet et al., 2021). In the studied area, both the frequencies of quantification and the concentrations of the considered antibiotics were usually higher in wastewater (Galindo and Ulia) than in the stations representing the receiving waters (E-N15, E-N17 and dL-UR20) (Fig. 2 and Table S4, in Supplementary material). The maximum concentrations of erythromycin (84 ng·L^{-1}), clarithromycin (535 ng·L^{-1}) and ciprofloxacin (802 ng·L^{-1}) were observed in the effluent of the WWTP of Galindo, and of azithromycin (672 ng·L^{-1}) in Ulia. In fact, effluents from WWTPs are considered one of the major pollution sources of antibiotics in estuarine and coastal environments since most WWTPs fail to eliminate them effectively (Biel-Maeso and Lara-Martín, 2021; Krzeminski et al., 2019; Langbehn et al., 2021; Wang et al., 2021; Zheng et al., 2021). In Galindo, the biggest WWTP in the Basque coast, a study was carried out in 2010 and 2011 to analyse >100 emerging pollutants. The removal efficiencies in secondary treatment effluents for antibiotics were estimated to be 32–66 %, and 71 % for ciprofloxacin (González et al., 2018).

However, azithromycin in wastewater (Galindo and Ulia) showed concentrations below the limit of quantification in 2020 (see Figs. S2 and S3, in Supplementary material). The matrix characteristics of these particular samples may have inhibited the MS signal detection of these compounds. Analysis of additional samples collected from 2021 onwards can shed light on this particular finding.

On the other hand, higher concentrations of ciprofloxacin were observed in the receiving water of the effluent of the Loiola WWTP (L-UR20), than in the wastewater (Ulia) (see Fig. S3 in Supplementary material). In 2021, some 28,000 heads of livestock were registered on farms in this area, Donostialdea, while there were about 17,000 of those in the Gran Bilbao area (Basque Statistics Institute, EUSTAT; https://www.eustat.eus/elementos/ele0019300/cabezas-de-ganado-de-las-explotaciones-agrarias-de-la-ca-de-euskadi-por-territorio-historico-y-comarca-segun-especie-p/tbl0019352_c.html, last access 10 Jan 2022). Since ciprofloxacin is a degradation product of enrofloxacin, used in animal health, and it will be found in waste water of animal farms (Loos et al., 2018), this activity could be considered as a diffuse source of ciprofloxacin to the coastal area where L-UR20 sampling site is located.

3.3. Temporal variation of antibiotics

Both the frequencies of quantification (Table S3, in Supplementary material) and the annual mean concentrations of the considered antibiotics (Fig. 3) showed, in general, a decrease along the study period, except for clarithromycin mainly in wastewater. The latter could be related to a higher consumption of clarithromycin in 2020 than in the previous years in the study area, but no data is available on the use of this antibiotic individually. However, although a general decrease was observed, a very short period of time has been considered, so the results should be taken with caution in this regard.

In order to reduce the sources of contamination of these substances to the environment, the reduction in consumption of human and veterinary

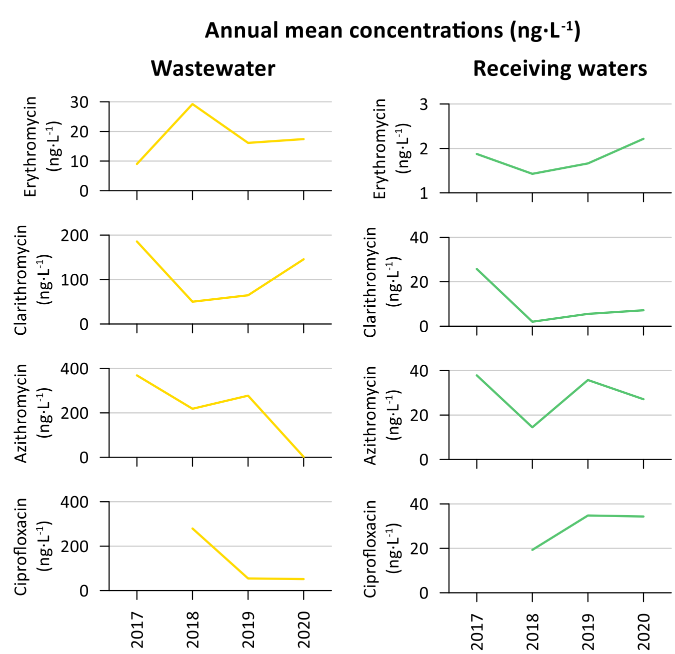

Fig. 3. Variation of annual mean concentrations (ng·L^{-1}) of antibiotics determined in the Basque coast from 2017 to 2020.

pharmaceuticals is needed, so surveys on their prescription habits or selling data can bring useful information (Branchet et al., 2021). In fact, the general decrease observed in the waters sampled in the Basque coast is consistent with the available results from the National Antibiotic Resistance Plan (PRAN; https://resistenciaantibioticos.es/es/profesionales/vigilancia/mapas-de-consumo/, last access 17 Jan 2022), which show a decrease in the consumption of systemic antibiotics (J01), macrolide antibiotics (J01FA; including azithromycin, clarithromycin and erythromycin) and fluoroquinolones (J01MA; including ciprofloxacin) in the Spanish primary care since 2015 (Fig. 4). Although annual data for the use of macrolides (J01FA) and fluoroquinolones (J01FM) in Basque primary care are not available, data for macrolides, lincosamides and streptogramins (J01F), and quinolones (J01M) also decreased in 2020, as do systemic antibiotics (J01) in general (Fig. 4).

Concerning the use of antibiotics in hospitals, the consumption of systemic antibiotics (J01) and fluoroquinolones (J01MA) has decreased in both Spanish and Basque hospitals in recent years (Fig. 4), as it has in primary care. However, the use of macrolides (J01FA) increased in hospitals in 2020, because of the significant rise in antibiotic consumption occurred during the first wave of the pandemic generated by the SARS-CoV-2 virus, known as COVID-19 (Fig. 4). According to PRAN analyses, the increase of antibiotic consumption in hospital in March 2020 (Fig. 4) was due to diagnostic uncertainty at the start of the pandemic. Despite being a viral infection and, therefore, neither treatable nor preventable with antibiotics, in several diagnosed patients in whom there was confirmation or high suspicion of bacterial co-infection or superinfection, COVID-19 was treated with antibiotic therapy according to established clinical management protocols (macrolides and 3rd generation cephalosporins) (Domingo-Echaburu et al., 2022; Echarte-Morales et al., 2021; Morales-Paredes et al., 2022; Morán Blanco et al., 2021; Pani et al., 2020). This increase in macrolide antibiotic consumption in March and April 2020 in hospitals in Spain is not generally reflected in the results obtained in the waters sampled on the Basque coast (Figs. S2 and S3, in Supplementary material). The decrease in primary care activity during lockdown could prompted a reduction in antibiotic consumption in April–May 2020 (Fig. 4), which could counterbalance the increase observed in hospital consumption.

On the other hand, according to data available in the ESVAC (European Surveillance of Veterinary Antimicrobial Consumption) database, sales of veterinary medicines containing antibiotics in their composition showed a reduction of 62 % in overall consumption in Spain from 2015 (402.0 mg·PCU^{-1}; mg of active ingredient per population correction unit) to 2020 (154.3 mg·PCU^{-1}). Sales of macrolides and fluoroquinolones have also decreased from 23.71 mg·PCU^{-1} in 2015, to 11 mg·PCU^{-1} in 2020, and from 8.96 mg·PCU^{-1} in 2014 to 3.7 mg·PCU^{-1} in 2020, respectively (Fig. 5).

3.4. RQ assessment in receiving waters

The RQs of each considered antibiotic calculated in all receiving water samples taken between 2017 and 2020 showed low risk for erythromycin

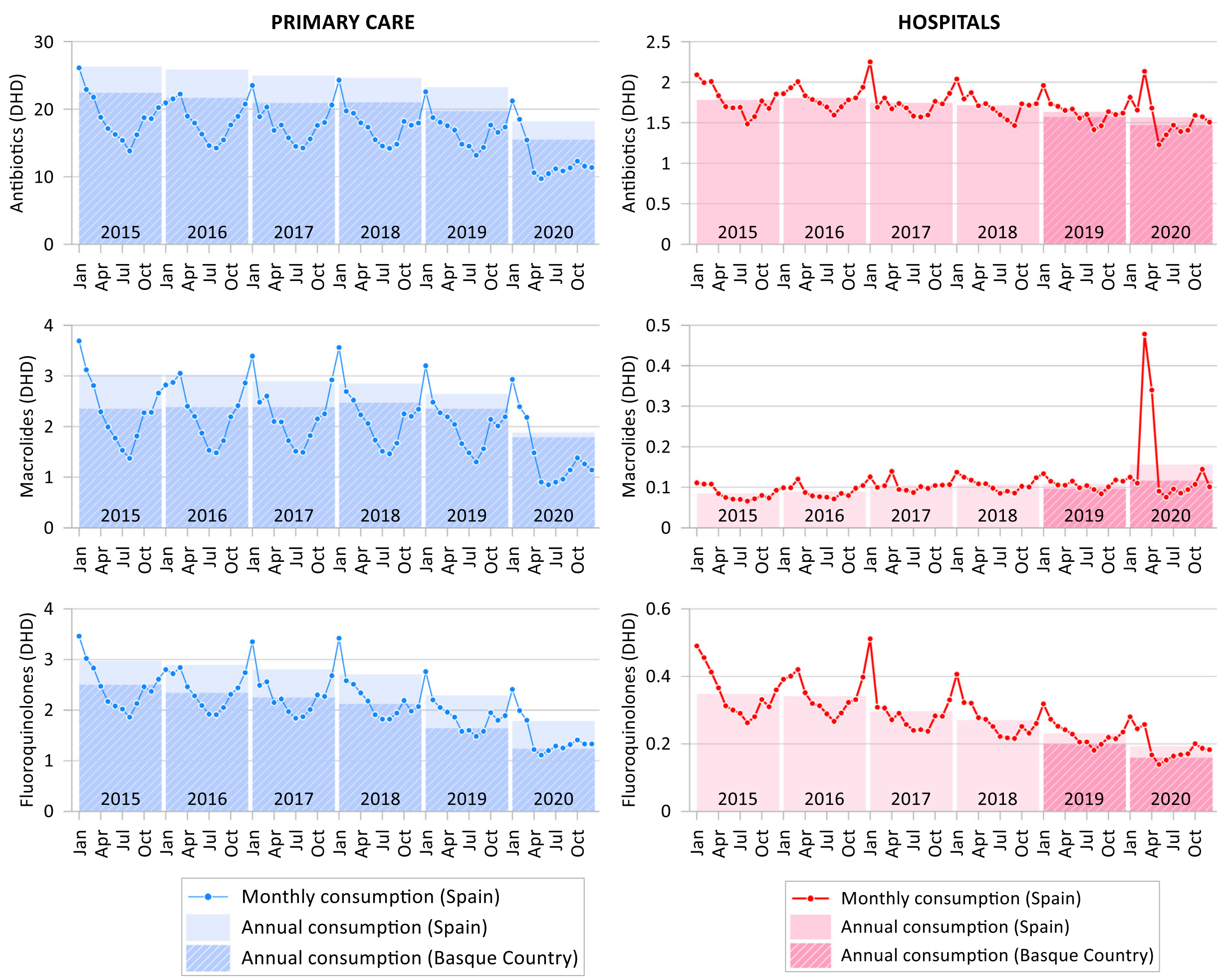

Fig. 4. Consumption of systemic antibiotics (J01), macrolide antibiotics (J01FA) and fluoroquinolones (J01MA) in Spanish and Basque Primary Care and Hospitals, between 2015 and 2020. DHD: Defined Daily Doses per 1000 inhabitants per day. Source: https://resistenciaantibioticos.es/es/profesionales/vigilancia/mapas-de-consumo/, last access 17 Jan 2022. There is no data available for annual consumption of macrolides (J01FA) and fluoroquinolones (J01MA) in the Basque primary care, so data for macrolides, lincosamides and streptogramins (J01F) and quinolones (J01M) are represented.

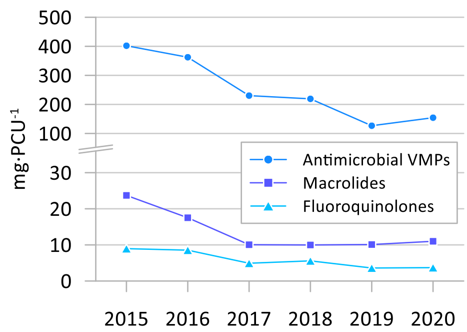

Fig. 5. Annual sales of antimicrobial veterinary medicinal products (VMP), macrolides and fluoroquinolones for food-producing animals, in mg·PCU^{-1}, in Spain, from 2015 to 2020. PCU: Population Correction Unit. Source: https://www.ema.europa.eu/en/veterinary-regulatory/overview/antimicrobial-resistance/european-surveillance-veterinary-antimicrobial-consumption-esvac, last access 17 Jan 2022.

in the receiving environment (Fig. 6), as did clarithromycin at stations E-N15 and L-UR20. Although clarithromycin in station E-N17 and ciprofloxacin in stations E-N17 and L-UR20 could represent a high risk in the receiving environment, azithromycin was the substance that showed the highest potential to pose a risk to organisms, with 47 %, 67 % and 7 % of the receiving water samples in E-N15, E-N17 and L-UR20, respectively, showing high risk (RQ ≥ 1) due to its presence. This is the only analysed antibiotic that showed RQ values representing high risk when the annual mean concentration is considered to calculate the quotient (E-N15 and E-N17 stations; Table 2). Similarly, high risk by azithromycin was found in the Ebro Delta (Spain; Gusmaroli et al., 2019), using the same PNEC values as in the Basque coast, but not in Cadiz Bay- Gulf of Cadiz (Spain; Biel-Maeso et al., 2018), or in Laizhou Bay (China; Lu et al., 2022), where considered PNEC values were two orders of magnitude higher.

Although RQs allow the comparison between different compounds with different toxicities and exposure levels, normalizing measurement of risk, it should be mentioned that PNEC values used to calculate the RQs were derived mainly using freshwater species. Therefore, the risk estimations made in the present study should be interpreted with care since this approach is more indicated for assessing the environmental risk in freshwater, and quite limited for marine and coastal environments (Beiras, 2021; Lu et al., 2018; Lu et al., 2020). Future research is needed to get more results of ecological tests on different estuarine and marine organism that would lead to derive appropriate PNEC for this type of waters (Biel-Maeso et al., 2018; Kötke et al., 2019).

On the other hand, as mentioned before, quantified concentrations in the receiving waters of the Basque coast showed spatial and temporal variations, mainly in the Nerbioi interior water body. The concentrations causing the risk probably do not stably occur, so the risk varies depending on the probability of aquatic organisms to be exposed to potentially unsafe levels. However, the RQ does not reveal to what degree any of the chemicals might actually be harming aquatic organisms (Liu et al., 2020). Therefore, both concentration and frequency of concentrations above de PNEC (high risk) were considered to calculate the optimised risk quotient (RQ_f) of antibiotics.

Table 2
Risk ratio for antibiotics considering annual mean concentration (RQ (annual mean)), and optimised risk ratio (RQ_f) in stations representing receiving waters (E-N15, E-N17 and L-UR20), from 2017 to 2020. For RQ_f, in red, high risk ($RQ_f \geq 1$); in orange, moderate risk ($1 > RQ_f \geq 0.1$); in yellow, endurable risk ($0.1 > RQ_f \geq 0.01$); in green, negligible risk ($0.01 > RQ_f > 0$); and in blue, no risk ($RQ_f = 0$). For RQ, in red, high risk (RQ ≥ 1), in yellow, medium risk (1 > RQ ≥ 0.1) and in green, no risk (RQ < 0.1).

Substance	Sampling point	RQ (annual mean)				RQ_f			
		2017	2018	2019	2020	2017	2018	2019	2020
Erythromycin	E-N15	0.01	0.01	0.01	0.01	0.00	0.00	0.00	0.00
	E-N17	0.02	0.01	0.02	0.03	0.00	0.00	0.00	0.00
	L-UR20	0.00	0.01	0.00	0.00	0.00	0.00	0.00	0.00
Clarithromycin	E-N15	0.02	0.01	0.03	0.04	0.00	0.00	0.00	0.00
	E-N17	0.58	0.03	0.10	0.14	0.19	0.00	0.00	0.00
	L-UR20	0.04	0.01	0.00	0.00	0.00	0.00	0.00	0.00
Azithromycin	E-N15	1.50	0.81	1.11	0.87	0.50	0.20	0.83	0.43
	E-N17	4.18	0.83	4.43	3.24	2.78	0.21	4.43	2.43
	L-UR20	0.30	0.64	0.00	0.18	0.00	0.16	0.00	0.00
Ciprofloxacin	E-N15		0.00	0.34	0.11		0.00	0.00	0.00
	E-N17		0.02	0.49	0.38		0.00	0.12	0.10
	L-UR20		0.62	0.34	0.67		0.21	0.00	0.33

The risk assessment according to the RQ_f index also showed that azithromycin was the only substance in this group that poses a high risk to the environment (Table 2), but only at station E-N17, not at station E-N15 where RQ (annual mean) showed high risk. In accordance with the RQ_f index, ciprofloxacin could pose moderate risk at stations E-N17 (in 2019) and L-UR20 (in 2018 and 2020), and the risk was medium when RQ (annual mean) was considered (Table 2).

However, it should be noted that most toxicity studies for risk assessment are done for individual compounds, but substances do not appear alone in the environment. In fact, several studies have shown that concentrations of pharmaceuticals, and in particular drugs, have cumulative effects, so that individual concentrations of substances are lower than expected to cause effects, but the mixed presence of these substances in the environment can cause toxic effects (Branchet et al., 2021; DeLorenzo and Fleming, 2008; Santos et al., 2010), although much remains to be studied in this area.

4. Conclusions

The study of three macrolide antibiotics (erythromycin, clarithromycin, and azithromycin) included in the first and second Watch Lists (EC, 2015, 2018), and a fluoroquinolone (ciprofloxacin) included in the second Watch List (EC, 2018) and still considered in the third Watch List (EC, 2020), was carried out quarterly in the most populated environments of the Basque coast between 2017 and 2020. This sampling and analytical

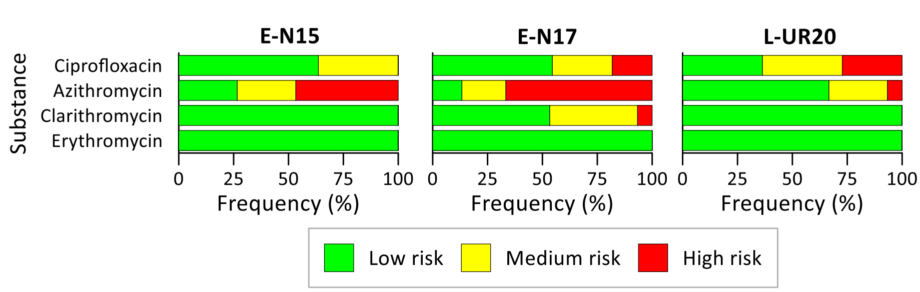

Fig. 6. Frequency of risk level (RQ) for antibiotics in stations representing receiving waters (E-N15, E-N17 and L-UR20), considering data from 2017 to 2020.

effort is a relevant contribution to determine their occurrence in wastewaters and receiving estuarine and coastal waters, and their possible environmental risks.

Frequencies of quantification and concentrations for the studied antibiotics showed a generalized decrease from 2017 to 2020, both in wastewater and in receiving water. There was also observed a decrease in the use of antibiotics in the primary care and in veterinary medicine, although the use of macrolide antibiotics in hospitals increased in the first quarter of 2020, probably due to the COVID-19 treatment.

Even being concentrations of the considered substances, in general, higher in wastewater effluents than in receiving waters, probably related to the dilution from the discharge points of the WWTPs, all the studied antibiotics, except erythromycin, exceeded the proposed PNEC in receiving waters, so they may pose a risk to the environment.

In the current pandemic situation, a variety of drugs have been used to alleviate the symptoms derived from the pandemic, including the substances studied in this study. This is an addition to the abusive use of antibiotics in medicine and veterinary medicine that has been made for a long time, leading to a state of bacterial resistance to these substances. The results obtained in this study show a decrease in the concentrations of these substances in the environment, so the different initiatives at European level to reduce the use of antibiotics (REDUCE, ESVAC etc.) seem to have been effective. However, they are still at levels that could generate a significant environmental risk, as in the case of azithromycin.

Therefore, although only ciprofloxacin is included in the 3rd Watch List, and since antibiotics are still widely used in human and veterinary medicine, this type of study confirms the need to continue monitoring these compounds in follow-up plans for a better evaluation of the environment in the Basque coast. In fact, macrolide antibiotics are currently being monitored in the Basque coast due to the importance that the Basque Water Agency has given to the continuous monitoring of these substances.

CRediT authorship contribution statement

Oihana Solaun: Conceptualization, Investigation, Visualization, Writing – original draft, Writing – review & editing. **José Germán Rodríguez:** Writing – review & editing. **Ángel Borja:** Writing – review & editing, Funding acquisition. **Ester López-García:** Investigation. **Bozo Zonja:** Investigation. **Cristina Postigo:** Investigation. **Damià Barceló:** Investigation. **Miren López de Alda:** Investigation, Writing – review & editing. **Joana Larreta:** Project administration, Investigation, Conceptualization, Writing – original draft, Supervision.

Data availability

Data will be made available on request.

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

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2022.157563.

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