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Occurrence of Antibiotics in Aqueous Matrices: An Outlook about the Situation in Brazil

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This review presents data regarding the occurrence of antibiotics in several aqueous matrices in Brazil reported in the last twelve years (from 2010 to 2022). Despite limited research on the topic, Brazil has the highest number of published data on antibiotics in surface water (SW) among Latin American countries. However, these studies primarily focused on the southern and southeastern regions, providing an incomplete picture of antibiotic occurrence in the aquatic environment of the country. Data from 24 papers show the detection of 23 antibiotics in 5 aquatic matrices, including drinking water, ranging from 0.13 ng L^{-1} to 37.30 μg L^{-1}. Occurrence in SW was the most reported, and sulfamethoxazole was the antibiotic most prevalent and concentrated in this matrix (7112.4 ng L^{-1}). Besides the fact that antibiotics are only partially removed in sewage treatment plants, in Brazil, only 55.8% of the sewage generated is collected, and 80.8% of the collected sewage is treated, which aggravates the release of antibiotics to the aquatic environment. This poses a significant concern due to potential harm to non-target organisms and antibiotic-resistant bacteria proliferation, worsening global antimicrobial resistance. Given this scenario, regular monitoring to assess the presence of antibiotics and resistant bacteria is crucial, enabling timely interventions and appropriate mitigation measures.

Keywords: emerging contaminants, pharmaceuticals, surface water, hospital wastewater, effluent

1. Introduction

The occurrence of the so-called contaminants of emerging concern (CECs) has attracted great attention in the last two decades due to the development of sensitive analytical methods that allow their detection. They include chemicals such as pharmaceuticals and personal care products, their metabolites, illicit drugs, pesticides, and disinfection by-products. However, no regulation has been discussed or proposed so far, despite the likely harmful effect on human health and aqueous organisms.[1-3]

According to the Brazilian Statistical Yearbook of the Pharmaceutical Market,[4] a growth of 7.9% was registered in 2019, indicating increasing consumption to mediate illnesses in both human and veterinary medicine.[5] In addition, the last report from IQVIA (IMS Quintiles Veritas)[6] estimates that the coronavirus disease (COVID-19) pandemic will expand globally the net cumulative pharmaceutical market in the period from 2020 to 2027 by $500 billion.

Antibiotics represent a class of pharmaceuticals produced both by living microorganisms or synthesized and are able to kill or hinder the development of pathogenic microorganisms. These compounds are widely used in medicine because they are indispensable in the battle against bacterial infections, mitigating complications, and fostering public health improvements by curtailing the transmission of infectious diseases. Moreover, antibiotics are extensively employed in agriculture to safeguard crops and livestock from bacterial ailments, thereby improving agricultural production and bolstering food security.[7,8]

According to the World Health Organization (WHO),[9] the total antibiotic consumption in Brazil was 22.8 DDD (defined daily doses) *per* 1000 inhabitants *per* day in 2016, the largest dose among the American countries in this report. Penicillins accounted for 53% of the total antibiotics consumption in Brazil, followed by macrolides/lincosamides/streptogramins, with 16%. Despite the drop in antibiotic consumption following restrictions on over-the-counter sales in 2010 in Brazil by a Federal law, sales increased again, however, at a notably lower rate.[10]

While antibiotics are crucial in medicine, their excessive consumption can stimulate the spread of antibiotic resistance, one of the principal threats to public health

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in the 21st century.[11,12] Furthermore, antibiotic resistant genes (ARGs) can be transferred from bacteria to bacteria as a way to survive in the presence of antibiotics.[13]

Antibiotics can reach the aqueous environment in different ways as depicted in Figure 1. Nevertheless, effluents from sewage treatment plants (STPs), pharmaceutical industry, and animal farming are the main sources of antibiotics discharged toward the natural waters.[7] In Brazil, hospital wastewaters (HWW) can be discharged into urban wastewater collection systems without specific limitations, given that they are considered domestic wastewater.[14] In addition, the discharge of untreated sewage directly into the environment is also an important source of antibiotics contamination.[15]

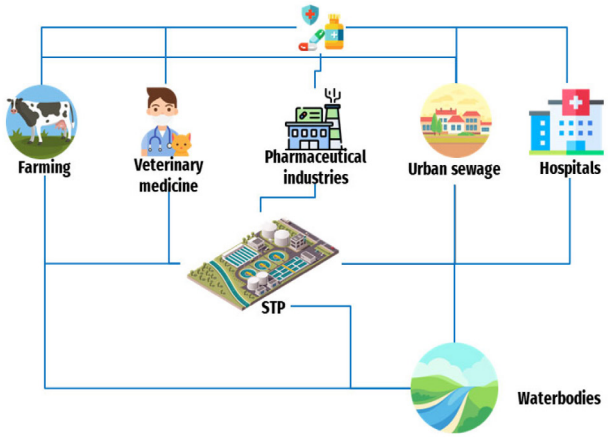

Figure 1. Main sources and fates of antibiotics in aquatic environment.

In STPs, the removal of micropollutants like pharmaceuticals is challenging compared to conventional macropollutants as highlighted by Verlicchi *et al.*[16] Owing to the vast range of properties exhibited by these drugs, such as solubility, polarity, and biodegradability, as well as the broad array of compounds they encompass, pharmaceuticals exhibit a wide range of removal rates without any discernible pattern, even among drugs belonging to the same therapeutic groups.[16-18] Pharmaceuticals can follow different pathways within the environment, such as retention in STP sludge, maintaining the original molecular structure and transformation into more hydrophilic compounds that remain persistent and ultimately end up in water bodies even after undergoing wastewater treatment.

The simultaneous presence of bacteria and antibiotics in wastewaters can lead to the development of ARGs, thereby increasing the survival of drug-resistant pathogens, as noted by Bougnom and Piddock.[13] Furthermore, the predominant use of biological treatments in STPs may contribute to the emergence of antibiotic-resistant pathogens due to their continued exposure to antibiotics in these plants.[19] This poses a considerable threat to human health and aquatic flora and fauna, highlighting the importance of addressing antibiotic contamination in aqueous matrices. To provide an overview of this issue, this review discusses the occurrence of the main types of antibiotics in different Brazilian aqueous matrices. By shedding light on these aspects, it is possible to better comprehend the extent of antibiotic contamination and its potential implications in the country.

2. Searching Approach

For this review, a search through relevant international databases and information sources such as *Science Direct*, *Web of Science* and *SciELO* was carried out to select relevant publications in this field. The following blends of keywords were used for the search: Brazil AND occurrence AND (pharmaceuticals OR antibiotics OR antimicrobials) AND (aqueous matrices OR surface water OR wastewater OR drinking water OR groundwater OR river water OR sea water).

Only antibiotics quantified in aqueous matrices were considered. Those that were merely detected without measurable concentrations were excluded (46 antibiotics). A total of 23 antibiotics were considered in this review: amoxicillin (AMX), ampicillin (AMP), azithromycin (AZT), cefaclor (CFC), cefapyrine (CFP), cefoperazone (CFZ), cephalexin (CFX), ciprofloxacin (CIP), clarithromycin (CLA), clindamycin (CLI), danofloxacin (DAN), doxycycline (DOX), enoxacin (ENO), enrofloxacin (ENR), erythromycin (ERY), norfloxacin (NOR), ofloxacin (OFO), oxytetracycline (OXY), sulfadiazine (SFD), sulfamethoxazole (SMX), sulfathiazole (STZ), tetracycline (TET), and trimethoprim (TMP).

3. Occurrence of Antibiotics in Different Aqueous Matrices in Brazil

The present review was constrained by a restricted collection of literature, as the search for pertinent sources yielded only 24 scientific papers. The low number of available papers in the literature proved that the data is insufficient to have an outlook with a good quality standard, given the huge Brazilian territory and population. Detailed information used for this review, including the class of the antibiotics, their levels of concentration, aqueous matrix, Brazilian regions, authors, and year of the publication are presented in Table 1.

One of the principal problems related to the low number of studies about the occurrence of antibiotics in Brazilian aquatic matrices is that these studies are concentrated in

the South and Southeast regions, mainly in São Paulo, Minas Gerais and Rio Grande do Sul states. From this search, only 2 studies were carried out in the Northeast region (Figure 2).

Considering that contamination of aqueous environment with antibiotics is in the level of ng L^{-1} to μg L^{-1}, studies on the occurrence of these contaminants demand expensive instrumentation such as mass spectrometry coupled to liquid chromatography (LC-MS) equipment to achieve low limits of quantification. Therefore, the larger infrastructure of research centers and universities in the South and Southeast regions of Brazil, probably contributed to the differences in the amount of data. These differences in infrastructure are a consequence of the presence of State funding agencies for research, which can finance the establishment of adequate analytical infrastructure and encourage studies to be carried out in these locations. Furthermore, the South and Southeast regions of Brazil are those with the largest population density and concentrate activities such as agriculture and industry and basic sanitation, which may increase concerns about the contamination of aquatic environments, including antibiotics. The absence of data in other regions (North and Central west) leaves Brazil without a general scenario about the occurrence of these contaminants in the aquatic environment.

Because of its huge territory (8.52 million km^2), Brazil shows variations in the pattern of pharmaceuticals consumption, which are influenced by diverse factors such as climate, demographic and social conditions.[44] It is important to highlight that the data available is only proper

Table 1. Occurrence of antibiotics in aqueous matrices in Brazil between 2010 and 2022

Compound (class)	Concentration range / (ng L^{-1})	n	Source	State	Region	Reference
Amoxicillin (penicillins)	180.00-4630.00	6	surface water	Paraná	South	Böger *et al.*[20]
	95.29-2234.66	4	surface water	Minas Gerais	Southeast	Gomes *et al.*[21]
	< 0.14-1284.00	10	surface water	São Paulo	Southeast	Locatelli *et al.*[22]
	< 6.00-287.50	8	surface water	Rio de Janeiro	Southeast	Monteiro *et al.*[23]
	4.00-17.00	13	surface water	São Paulo	Southeast	Montagner *et al.*[24]
Ampicillin (penicillins)	< LOD-1.00	13	surface water	São Paulo	Southeast	Montagner *et al.*[24]
Azithromycin (macrolides)	136.8.00-691.50	4	STP effluent	Rio Grande do Sul	South	Ramalho *et al.*[25]
	60.00-650.00	6	surface water	Paraná	South	Böger *et al.*[20]
	< 10.00-158.00	48	surface water	Rio Grande do Sul	South	Arsand *et al.*[26]
	3.80-18.80	8	STP effluent	Rio Grande do Sul	South	Jank *et al.*[27]
	3.18-99.66	4	surface water	Minas Gerais	Southeast	Gomes *et al.*[21]
	< 10.00-49.90	20	surface water	Rio de Janeiro	Southeast	Bianco *et al.*[28]
	< 1.10-39.70	4	surface water	Rio Grande do Sul	South	Jank *et al.*[27]
Azithromycin (macrolides)	< 9.00-35.90	8	surface water	Rio de Janeiro	Southeast	Monteiro *et al.*[23]
Cefaclor (cephalosporins)	< 10.00-23.10	20	surface water	Rio de Janeiro	Southeast	Bianco *et al.*[28]
Cefapyrine (cephalosporins)	< 10.00-116.00	20	surface water	Rio de Janeiro	Southeast	Bianco *et al.*[28]
Cefoperazone (cephalosporins)	< 10.00-548.00	20	surface water	Rio de Janeiro	Southeast	Bianco *et al.*[28]
Cephalexin (cephalosporins)	< 0.19-2422.00	10	surface water	São Paulo	Southeast	Locatelli *et al.*[22]
	< 4.00-575.50	8	surface water	Rio de Janeiro	Southeast	Monteiro *et al.*[23]
	< 10.00-539.00	20	surface water	Rio de Janeiro	Southeast	Bianco *et al.*[28]
	46.60-518.70	8	STP effluent	Rio Grande do Sul	South	Jank *et al.*[27]
	< 10.00-179.00	48	surface water	Rio Grande do Sul	South	Arsand *et al.*[26]
	11.00-29.00	13	surface water	São Paulo	Southeast	Montagner *et al.*[24]
Ciprofloxacin (fluoroquinolones)	1300.00-33900.00	nr	hospital wastewater	São Paulo	Southeast	Rodrigues-Silva *et al.*[29]
	< 3.00-6730.00	10	STP effluent	São Paulo	Southeast	Marasco Júnior *et al.*[30]
	500.00-5600.0	nr	STP effluent	São Paulo	Southeast	Rodrigues-Silva *et al.*[29]

Table 1. Occurrence of antibiotics in aqueous matrices in Brazil between 2010 and 2022 (cont.)

Compound (class)	Concentration range / (ng L^{-1})	n	Source	State	Region	Reference
Ciprofloxacin (fluoroquinolones)	171.93-3993.61	4	surface water	Minas Gerais	Southeast Region	Gomes *et al.*[21]
	164.00-382.20	4	STP effluent	Rio Grande do Sul	South	Ramalho *et al.*[25]
	< 10.00-344.00	48	surface water	Rio Grande do Sul	South	Arsand *et al.*[26]
	< 2.10-169.20	8	STP effluent	Rio Grande do Sul	South	Jank *et al.*[27]
	< 0.13-119.00	10	surface water	São Paulo	Southeast	Locatelli *et al.*[22]
	64.00[a]	3	STP effluent	Rio Grande do Sul	South	Bisognin *et al.*[31]
	< 10.00-70.00	6	surface water	Paraná	South	Böger *et al.*[20]
	< 2.10-66.10	4	surface water	Rio Grande do Sul	South	Jank *et al.*[27]
	< LOQ-12.00	13	surface water	São Paulo	Southeast	Montagner *et al.*[24]
Clarithromycin (macrolides)	< 10.00-185.00	20	surface water	Rio de Janeiro	Southeast	Bianco *et al.*[28]
	< 12.70-168.00	12	surface water	Minas Gerais	Southeast	Reis *et al.*[32]
	< 6.00-39.20	8	surface water	Rio de Janeiro	Southeast	Monteiro *et al.*[23]
Clindamycin (lincosamides)	< 5.00-134.00	48	surface water	Rio Grande do Sul	South	Arsand *et al.*[26]
	99.00[a]	3	STP effluent	Rio Grande do Sul	South	Bisognin *et al.*[31]
Danofloxaxin (fluoroquinolones)	< 0.40-68.00	12	surface water	Minas Gerais	Southeast	Reis *et al.*[32]
	< 0.90-42.00	12	drinking water	Minas Gerais	Southeast	Reis *et al.*[32]
Doxycycline (tetracyclines)	0.13-0.67	4	surface water	Minas Gerais	Southeast	Gomes *et al.*[21]
Enoxacin (fluoroquinolones)	< 3.30-354.00	12	drinking water	Minas Gerais	Southeast	Reis *et al.*[32]
	< 10.00-219.00	12	surface water	Minas Gerais	Southeast	Reis *et al.*[32]
Enrofloxacin (fluoroquinolones)	73.20-566.00	4	surface water	Minas Gerais	Southeast	Gomes *et al.*[21]
	118.40-374.40	4	STP effluent	Rio Grande do Sul	South	Ramalho *et al.*[25]
	< 5.00-219.00	12	drinking water	Minas Gerais	Southeast	Reis *et al.*[32]
	200.00[a]	nr	surface water	Maranhão	Northeast	Dias *et al.*[33]
	120.00[a]	nr	sea water	Maranhão	Northeast	Dias *et al.*[33]
	< 1.20-64.00	12	surface water	Minas Gerais	Southeast	Reis *et al.*[32]
	< 1.20-14.00	4	surface water	nr	nr	Santos *et al.*[34]
Erythromycin (macrolides)	< 2.10-14500.00	8	STP effluent	Rio Grande do Sul	South	Jank *et al.*[27]
	225.55-683.77	4	surface water	Minas Gerais	Southeast	Gomes *et al.*[21]
Norfloxacin (fluoroquinolones)	< 3.00-5570.00	10	STP effluent	São Paulo	Southeast	Marasco Júnior *et al.*[30]
	800.00-4400.00	nr	hospital wastewater	São Paulo	Southeast	Rodrigues-Silva *et al.*[29]
	29.00-292.00	48	surface water	Rio Grande do Sul	South	Arsand *et al.*[26]
	< 1.00-210.00	12	drinking water	Minas Gerais	Southeast	Reis *et al.*[32]
Norfloxacin (fluoroquinolones)	< 0.70-156.00	12	surface water	Minas Gerais	Southeast	Reis *et al.*[32]
	< 10.00-130.00	6	surface water	Paraná	South	Böger *et al.*[20]
	< 0.70-130.00	4	surface water	nr	nr	Santos *et al.*[34]
	6.70-100.00	8	STP effluent	Rio Grande do Sul	South	Jank *et al.*[27]
	< 3.70-54.40	4	surface water	Rio Grande do Sul	South	Jank *et al.*[27]
	< 0.13-51.00	10	surface water	São Paulo	Southeast	Locatelli *et al.*[22]
	8.00-26.00	6	surface water	São Paulo	Southeast	Torres *et al.*[35]
	< LOD-4.00	13	surface water	São Paulo	Southeast	Montagner *et al.*[24]
Ofloxacin (fluoroquinolones)	900.00-27100.00	nr	hospital wastewater	Campinas	Southeast	Rodrigues-Silva *et al.*[29]
	34.00[a]	3	STP effluent	Porto Alegre	South	Bisognin *et al.*[31]
Oxytetracycline (tetracycline)	1154.00[a]	1	STP effluent	Rio Grande do Sul	South	Bisognin *et al.*[31]
	< 6.09-44.10	24	surface water	Rio de Janeiro	Southeast	Monteiro *et al.*[36]

Table 1. Occurrence of antibiotics in aqueous matrices in Brazil between 2010 and 2022 (cont.)

Compound (class)	Concentration range / (ng L^{-1})	n	Source	State	Region	Reference
Sulfadiazine (sulfonamides)	< 5.00-120.00	48	surface water	Rio Grande do Sul	South	Arsand *et al.*[26]
	3.55-85.00	4	surface water	Minas Gerais	Southeast	Gomes *et al.*[21]
	51.00[a]	3	STP effluent	Rio Grande do Sul	South	Bisognin *et al.*[31]
Sulfamethoxazole (sulfonamides)	12500.00-37300.00	7	hospital wastewater	Rio Grande do Sul	South	Brenner *et al.*[37]
	332.78-7112.44	4	surface water	Minas Gerais	Southeast	Gomes *et al.*[21]
Sulfamethoxazole (sulfonamides)	< 20.00-2420.00	12	surface water	Rio de Janeiro	Southeast	Sabino *et al.*[38]
	< 10.00-1800.00	6	surface water	Paraná	South	Böger *et al.*[20]
	7.40-931.00	8	STP effluent	Rio Grande do Sul	South	Jank *et al.*[27]
	< 2.74-572.00	4	surface water	Rio Grande do Sul	South	Jank *et al.*[27]
	< 2.62-467.00	24	surface water	Rio de Janeiro	Southeast	Monteiro *et al.*[36]
	< 10.00-340.50	20	surface water	Rio de Janeiro	Southeast	Bianco *et al.*[28]
	301.00[a]	3	STP effluent	Rio Grande do Sul	South	Bisognin *et al.*[31]
	34.00-184.00	48	surface water	Rio Grande do Sul	South	Arsand *et al.*[26]
	< 7.00-120.00	28	surface water	Maranhão	Northeast	Chaves *et al.*[39]
	< 0.24-106.00	10	surface water	São Paulo	Southeast	Locatelli *et al.*[22]
	< 9.00-105.00	8	surface water	Rio de Janeiro	Southeast	Monteiro *et al.*[23]
	< 5.00-100.00	4	STP effluent	Rio Grande do Sul	South	Ramalho *et al.*[25]
	< 1.50-56.80	3	STP effluent	Minas Gerais	Southeast	Brandt *et al.*[40]
	17.50[a]	13	surface water	Paraná	South	Fazolo *et al.*[41]
	< 10.00-12.50	11	drinking water	Rio de Janeiro	Southeast	Bianco *et al.*[28]
	2.70-9.91	46	surface water	Minas Gerais	Southeast	Rodrigues *et al.*[42]
	< LOD-2.00	13	surface water	São Paulo	Southeast	Montagner *et al.*[24]
Sulfathiazole (sulfonamides)	70.00[a]	1	STP effluent	Rio Grande do Sul	South	Bisognin *et al.*[31]
Tetracycline (tetracyclines)	< 2.40-32.30	8	STP effluent	Rio Grande do Sul	South	Jank *et al.*[27]
	< 0.76-11.00	10	surface water	São Paulo	Southeast	Locatelli *et al.*[22]
Trimethoprim (trimethoprim)	2650.00-11300.00	7	hospital wastewater	Rio Grande do Sul	South	Brenner *et al.*[37]
	63.10-3442.00	8	STP effluent	Rio Grande do Sul	South	Jank *et al.*[27]
	< 0.25-484.00	10	surface water	São Paulo	Southeast	Locatelli *et al.*[22]
	8.08-322.98	46	surface water	Minas Gerais	Southeast	Rodrigues *et al.*[42]
	< 1.20-123.7	12	surface water	Minas Gerais	Southeast	de Barros *et al.*[43]
	< 0.50-93.70	4	surface water	Rio Grande do Sul	South	Jank *et al.*[27]
	20.00-84.00	48	surface water	Rio Grande do Sul	South	Arsand *et al.*[26]
	< 20.00-60.00	12	surface water	Rio de Janeiro	Southeast	Sabino *et al.*[38]
	< 1.00-57.00	3	STP effluent	Minas Gerais	Southeast	Brandt *et al.*[40]
	50.00[a]	3	STP effluent	Rio Grande do Sul	South	Bisognin *et al.*[31]
	1.00-7.00	13	surface water	São Paulo	Southeast	Montagner *et al.*[24]

[a]Concentration range was not provided. n: distribution size of data; STP: sewage treatment plant; nr: not reported; LOD: limit of detection; LOQ: limit of quantification.

to represent these regions and is not an appropriate standard for the rest of the country.

The occurrence of antibiotics was mainly reported in surface water (SW), followed by STP effluents, HWW, drinking water (DW) and sea water, with 18 studies carried out in SW (Figure 3).

A total of 24 antibiotics were detected in 5 different aquatic matrices. Because of the higher number of studies in SW, most of the antibiotics were found in this matrix (Figure 4).

Considering the three most studied matrices, SW, STP effluent, and HWW, only CIP, NOR, SMX, and TMP were

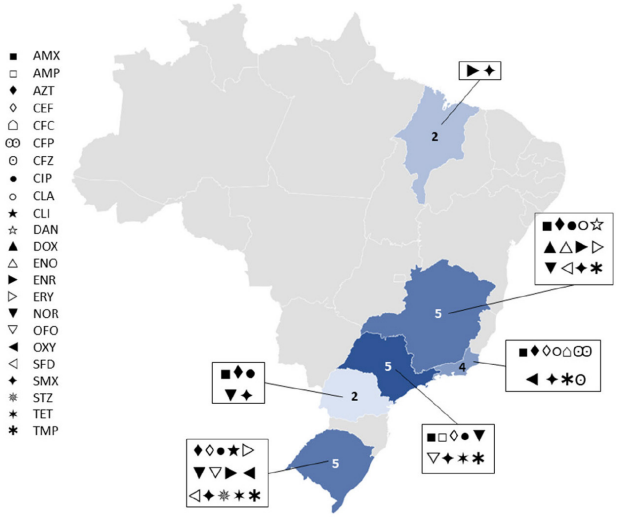

Figure 2. Brazilian regions where the occurrence of different antibiotics in the aquatic environment were reported.

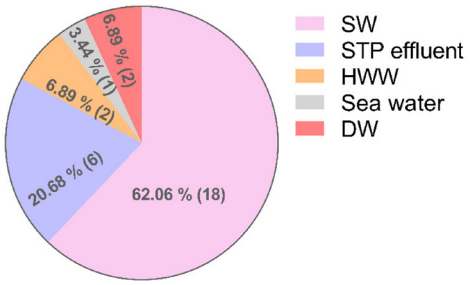

Figure 3. Distribution of matrices studied according to the papers reported.

found in all of these matrices. SMX was the antibiotic detected at the highest concentration, 37300 ng L^{-1} in HWW (Figure 5), the most frequently detected, and the only antibiotic found in all the states studied. Of the 16 papers that studied SMX, all of them found it with measurable concentration (100% frequency) in contrast with CIP, NOR, and TMP, highly studied but found at lower frequency (Figure 6). These data show the different scenarios of contamination by antibiotics in the different aqueous matrices and Brazilian regions, that will be discussed in the next sections.

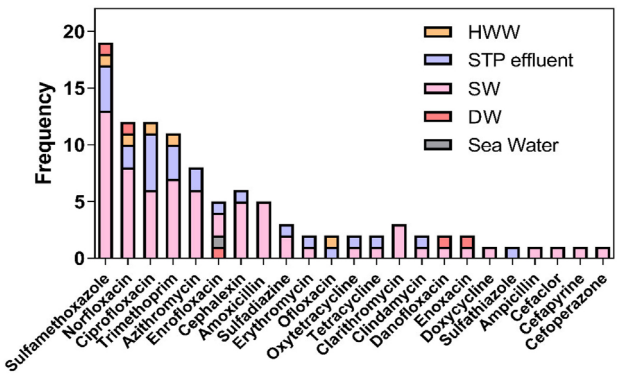

Figure 4. Frequency of antibiotic occurrence according to the aqueous matrix.

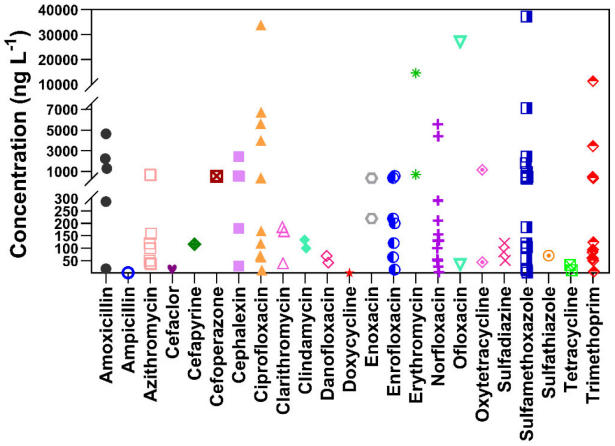

Figure 5. Maximum antibiotic concentrations found in all matrices.

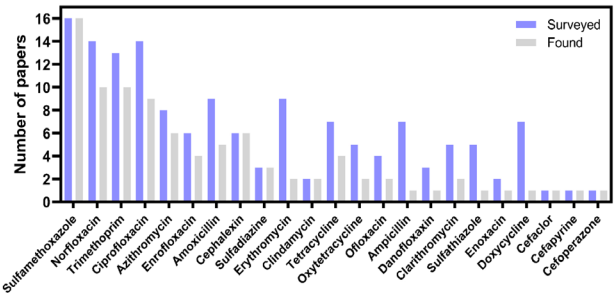

Figure 6. Overall detection frequencies for the antibiotics found in aqueous matrices in Brazil.

3.1. Sewage treatment plant effluent

Conventional STPs were not designed to remove antibiotics since most are based on biological degradation using a pool of microorganisms for the removal of biodegradable organic matter, nitrogen and phosphorous.[45] Due to the nature and structure of the antibiotics, their removal in STPs can vary widely depending on several factors such as the complexity of the structure and the physicochemical characteristics of antibiotics and the process applied.[46]

The occurrence and removal of antibiotics in STP in Brazil were reported in six studies. Bisognin *et al.*[31] showed the difficulty of antibiotics removal in STP even when using different treatment stages and processes such as Upflow Anaerobic Sludge Blanket (UASB), activated sludge, the cyclic treatment of the aeration stage and hydrogen peroxide disinfection. Among the eleven antibiotics detected in the influent, only two were not detected in the effluent. They also showed that some antibiotics may undergo microbial degradation (ENR, SMX, STZ), while others are removed by adsorption (TET, NOR and DOX) or may be recalcitrant (TMP, CLI, STZ, SFD and OXY).

Jank *et al.*[27] examined the occurrence of eight antibiotics (AZT, CFX, CIP, ERY, NOR, SMX, TET, and TMP) in the

influent and effluent of a STP based on activated sludge over a period of eight months. It was found that while the concentrations of antibiotics in the effluent were lower than in the influent, all eight antibiotics were still detected at the outlet of the STP at a concentration range from 3.8 to 14,500 ng L^{-1}. Among the detected antibiotics, SMX and TMP were the most frequently detected and at the highest average concentrations. The removal efficiency ranged from complete removal for CIP, ERY, and TET to negative for CIP, ERY, CFX, TRI and AZY.

One of the most important causes of the negative removal rates is the presence of metabolites that can pass through the retransformation (deconjugation processes) in the STP.[47,48] As a result, STP can contribute to the release of antibiotics in natural waters not only due to the inefficiency of removal but also owing to the biotransformation process during the biological treatment. Nevertheless, it is crucial to highlight that this negative rate could also stem from the matrix effect during antibiotic analysis, a phenomenon capable of altering responses, suppressing or improving the analyte response in techniques like electrospray mass spectrometry.[49]

According to data provided by IQVIA Brazil,[50] São Paulo state consumed 5.4 and 4.3 million boxes of AZT and CFX, respectively, the most used antibiotics in 2020, while only 0.8 million of a combination of SMX and TMP was sold. However, SMX is the antibiotic most frequently found in SW. One of the reasons can be the variability in the efficiency of the STP to remove different antibiotics.

The β-lactam ring in the CFX structure is susceptible to hydrolysis, showing its poor stability under environmental conditions.[27] It is also noted that CFX is well removed in STP, while SMX remains in the effluent even after the treatment. These data indicate that SMX is more hardly removed during the conventional activated sludge process and can be also persistent in the aqueous environment and more frequently detected.

Other reasons for the frequency of detection of SMX are the amount of the antibiotic that is excreted unchanged, and the frequency it is chosen as target in studies concerning aqueous environment contamination.

CFX is excreted mostly as the parent compound, around 80%, while SMX only 15%.[51] However, while CFX is susceptible to indirect photolysis during the treatment,[52] SMX can be more persistent in the STP.[53,54]

The increased persistence of SMX can be partially attributed to the formation of resistant photoproducts during the solar photolysis in STP that employ stabilization pounds, which can undergo retransformation during the biodegradation process.[53] Additionally, metabolites of SMX, such as *N*4-acetyl-sulfamethoxazole, an acetylated derivative, can also pass through retransformation during the biological process in the STP, causing higher SMX concentration in the effluent compared to the influent concentrations.[47]

3.2. Hospital wastewater (HWW)

Only two studies reported antibiotics monitoring in HWW in Brazil. Brenner *et al.*[37] reported the presence of SMX and TMP, an important association of antibiotics, and their metabolites, in an effluent from the Hospital of University of Santa Maria, in which the maximum concentrations found were 37,300 ng L^{-1} of SMX and 11,300 ng L^{-1} of TMP, the highest concentrations of these antibiotics determined among all studies reviewed.

Rodrigues-Silva *et al.*[29] investigated the presence of fluoroquinolones in raw and treated HWW using the UASB system for six months. The HWW raw samples presented a higher concentration of fluoroquinolones when compared to the treated HWW. Three fluoroquinolones were detected in the raw HWW, with CIP and OFX present in all samples at the highest concentration, 1,300-33,900 and 900-27,100 ng L^{-1}, respectively, while concentrations of NOR varied from 800 to 4,400 ng L^{-1} present in only 17% of the samples analyzed. Among the antibiotics studied, CIP was the only one detected in the treated HWW samples, at a lower frequency and concentration (500-5,600 ng L^{-1}) when compared to the HWW raw samples, showing that conventional treatment system applied removed only partially the antibiotics belonging to this particular class. It is important to point out that the highest concentrations of SMX, CIP and OFX were found in HWW, making this matrix a potential spot of antibiotics when no adequate STP is applied.

3.3. Surface and drinking water

Most data on antibiotics occurrence were obtained in SWs, where 21 different antibiotics were found, with SMX, AMX, CIP, and CFX at concentrations above 1,000 ng L^{-1} in the states of Minas Gerais, São Paulo, Paraná, and Rio de Janeiro.

The elevated levels of antibiotics may be associated with the discharge of treated or untreated wastewater into SW bodies. This can be attributed to the fact that, as *per* the Brazilian Diagnostic of Water and Sewage Services,[55] only 55.8% of the overall population exhibits access to collected sewage, with a mere 80.8% of the aforementioned collected sewage undergoing treatment.

In Rio de Janeiro, the João Mendes River receives untreated sewage, which may explain the presence of

antibiotics, with SMX at concentrations exceeding 2,000 ng L^{-1} in the water.[38] Similarly, in Paraná and Minas Gerais, studies[20,21] suggest that higher antibiotic concentrations correlate with contamination from domestic effluent. Likewise, in the state of São Paulo, the highest concentration of CFX was found in a sample from a polluted river that receives about 25% of raw sewage discharge.[22]

This raises the question of knowing whether some of the studied samples come from rivers that are urban supply points or influents of water treatment plants, creating a cycle of contamination with these antibiotics.

While the existence of a contamination cycle could not be confirmed in any of the studies, Jank *et al.*[27] observed the presence of antibiotics in SW and samples collected from a STP that discharges its effluent into the Guaíba River, which is the source of supply water for the city of Porto Alegre.

Another study[25] conducted in Porto Alegre assessed the presence of antibiotics in samples from STP and drinking water treatment plant (DWTP) before and after treatment. The results demonstrated that even with the presence of antibiotics in STP effluents and DWTP influents, the treatment process applied at the DWTP efficiently removed these compounds from the water, with no detection of antibiotic residues in the potable water. However, in two other studies carried out in Rio de Janeiro, the antibiotics CLA, SMX and AZT were detected in drinking water, albeit in low concentrations, reaching levels of up to 50 ng L^{-1}.[23,28]

Antibiotics such as ENO and ENR were also quantified in DW in Minas Gerais, at much higher concentration, 219 ng L^{-1}, and DAN and NOR with 42 and 210 ng L^{-1}, respectively.[32] SMX was also found in drinking water in Rio de Janeiro at concentrations of 12.5 ng L^{-1}.[28] As discussed by de Aquino *et al.*,[15] despite the low concentrations of antibiotics detected in drinking water, certain antibiotics may still present a notable risk to human health. Moreover, even at low concentrations, antibiotics can represent a direct risk to the environment, and an indirect risk to the population by contributing to the development of bacterial resistance.

Among the environmental impacts of antibiotics, antimicrobial resistance and transfer of antibiotic-resistant genes, and ecotoxic effects on non-target organisms are receiving attention from an environmental and public health perspective.[8]

Despite the low number of studies, the reported data indicates high levels of antibiotics in Brazil's SWs compared to studies conducted in other countries such as Mexico, Germany and China.[56-58] Antibiotics such as SMX, AMX, CIP and CFX were found at concentrations > 1 μg L^{-1} that can pose potential risks to the aqueous biota and lead to serious human health problems.

According to Holten *et al.*,[59] the 50% effect concentration (EC_{50}) of AMX to the freshwater cyanobacterium *Microcystis aeruginosa* is 3.7 μg L^{-1}. As reported by Boger *et al.*[20] AMX was found in Barigui River at 4.6 μg L^{-1} indicating a potential toxic effect of this environmentally relevant concentration. The authors also verified a correlation of the presence of resistant bacteria, which were found in all samples, with the occurrence of the antibiotics AMX, AZT, CIP, NOR and SMX in river water. Among the coliform bacteria tested, *Escherichia coli* was the most resistant bacteria, while resistance profile was constant against AMX, SMX, NOR, and CIP during the sampling period. However, resistance to DOX was not constant, probably due to its lower concentration, < limit of quantification (LOQ, 0.2 μg L^{-1}) when compared to the other investigated antibiotics.

These data suggest that the concentration of antibiotics in Brazilian surface waters can have toxic effect against nontarget aquatic organisms and that antibiotic resistance can be a consequence of the low persistent antibiotic concentrations in the river water. In a recent paper, Barán *et al.*[60] investigated the occurrence of CECs in Brazil, including antibiotics, and evaluated their environmental risk. The risk assessment based on Brazilian data was expressed in terms of risk quotients (RQ). For TMP and SMX, the environmental risk was considered high in all dilution scenarios analyzed.

3.4. Seasonal variation

Some of the studies discussed in this review have investigated the impact of seasonal variation on the occurrence of antibiotics in aquatic matrices, since high temperatures, solar irradiance and rainy periods can contribute to the intensification of compounds decomposition including pharmaceuticals.[61] Evaluation of the seasonal variation of antibiotics occurrence in aquatic matrices has revealed higher concentrations in winter and lower concentrations in summer in Brazil.

Basically, in the summer, the higher temperatures lead to the intensification of the biodegradation, while high solar irradiance may also promote photolysis, which associated with the higher precipitation levels, results in lower concentrations than in winter.

In South and Southeast regions of Brazil, the climate is characterized by rainy summers and dry winters.[62] As a consequence, the higher precipitation in the summer leads to dilution and consequently lower antibiotic concentrations.[27,32]

Furthermore, winter months are associated with the increase in the incidence of respiratory infections. Consequently, the consumption of antimicrobials to treat respiratory diseases increases considerably, resulting in the occurrence of higher levels of antibiotics in aqueous matrices. The antimicrobials commonly prescribed to treat respiratory diseases were found at higher concentrations in the winter period in influent and effluent samples from sewage treatment plants when compared to the antibiotics generally used for urinary and other infections, which are generally climate independent.[27]

As a contrast, in a study conducted by Chaves *et al*.[39] in São Luis, in the northeast of Brazil, where the climate is quite different from the southeast, during July (rainy season), some pharmaceuticals were found at higher concentrations in water samples compared to December (dry season), indicating that the dilution caused by the rainy period did not play an important role in the occurrence of these compounds in SW in that region.

4. Occurrence of Antibiotics Worldwide

Although the low amount of research regarding this subject, Brazil is still the Latin American country with the highest number of published data on the occurrence of pharmaceuticals in water bodies. This information is supported by a review published in 2019,[63] that analyzed studies conducted in several Latin American countries, including Brazil, Argentina, Chile, Colombia and Mexico, and found that although there were studies conducted in these countries, Brazil had the highest number of published studies on the occurrence of CECs, including antibiotics, in different environmental matrices.

Mexico stands out as the second Latin American country with the highest amount of occurrence data for pharmaceuticals in aquatic matrices.[63] However, regarding antibiotics, few studies evaluated the presence of these compounds in aquatic bodies. Lesser *et al*.[58] found 9 types of antibiotics in SWs at concentrations ranging from 0.56 to 46.6 ng L^{-1}. Rivera-Jaimes *et al*.[64] found just SMX and TMP in STP effluents and SW at concentrations ranging from 34 to 2010 ng L^{-1}. Although these concentrations are lower than most found in Brazil, the lack of data on the occurrence of antibiotics in aquatic matrices prevents the comparison between the two countries, as well as with other Latin American countries.

Concentrations of antibiotics have been detected in SW in other countries, with levels ranging from 509 to 13,765 ng L^{-1} in Kenya,[65,66] 2.7 to 2861 ng L^{-1} in Ghana,[67] 1.4 to 14331 ng L^{-1} in South Africa,[65,68] 2.3 to 101 ng L^{-1} in Germany,[56,69-72] 1.7 to 740 ng L^{-1} in Spain,[73,74] 0.2 to 892.29 ng L^{-1} in China,[57,75-77] and 0.9 to 1435 ng L^{-1} in France.[78-80]

The concentrations in STP effluents ranged from 66 to 3,336 ng L^{-1} in Kenya,[66] 78 to 8,263 ng L^{-1} in Germany,[70,71,81,82] 7.0 to 2,250 ng L^{-1} in Spain[73,83-85] and 13 to 499 ng L^{-1} in Italy.[86] The antibiotics were also found in DW in Spain,[73] and groundwater in France[78] with concentrations ranging from 0.5 to 32.9 ng L^{-1}.

Based solely on the SW data analyzed in this study, which was the most studied matrix, it is evident that the levels of antibiotics detected in Brazilian SWs are among the highest in the world, ranging from 0.67 to 7,112.44 ng L^{-1}, lower only than in Kenya and South Africa.

The high variation of antibiotic levels in different countries can be attributed to several factors, including the country's income, the presence of sewage treatment systems, and access to the healthcare system. Specifically, high-income countries have a higher proportion of sewage treatment plants installed, which can significantly reduce the presence of antibiotics in the aquatic environment. In contrast, low- and middle-income countries often have a lower proportion of sewage treatment or use inadequate treatment processes, contributing to the release of contaminants into aqueous environment, especially antibiotics with complex structures and low biodegradability. Additionally, self-medication and the purchase of cheaper antibiotics such as SMX may be more common in low-income countries with limited access to healthcare.[65]

5. Brazilian Legislation

There are currently no specific regulations worldwide that set concentration limits in water bodies for the antibiotics prescribed in human medicine, or that ensure antibiotics are properly removed from wastewater before discharge to SWs. However, some countries have monitoring lists or guide values for antibiotic limits regarding DW quality.[17]

In the United States, the Environmental Protection Agency (EPA) has set maximum allowed concentrations for various substances in DW, including pharmaceuticals. These standards, known as maximum contaminant levels (MCLs), are intended to ensure that DW is safe for human consumption. While the EPA has not established an MCL specifically for antibiotics, erythromycin has entered Contaminant Candidate List 4 (CCL 4), which contains contaminants that do not yet have regulation but may require future regulation under the Safe Drinking Water Act.[87]

In addition to the United States, the European Union (EU) maintains a list of substances known as the Watch List (WL), which includes potential water pollutants

that should be carefully monitored to determine the risk they pose to the aquatic environment and whether limits should be set. The Watch List includes CECs such as antibiotics.[88]

In Australia, there is no monitoring list, but Australian Guidelines for Water Recycling were created to provide guidance on the use of recycled wastewater to increase the availability of clean DW. These guidelines address microbial and chemical concerns, including pharmaceuticals, and provide recommendations for safe levels of CECs, such as antibiotics, based on their potential impact on human health.[89]

Unfortunately, Brazil is experiencing a significant delay in addressing the issue of CECs levels in water matrices. There is no national legislation, monitoring lists or guide values that limits CECs levels in surface water, including antibiotics, or in wastewater before discharging into SW. In fact, a Federal resolution of environmental council number 357/2005[90] establishes the conditions and standards for discharge of effluents into SW. Although this resolution establishes limits and control measures for multiple pollutants, it does not incorporate specific provisions for the regulation of pharmaceutical drug release into the environment.

Therefore, the lack of information about occurrence of antibiotics and other pharmaceuticals in Brazil is in part due to the absence of specific guidelines. The establishment of laws or guidelines can promote the surveillance of environmental contaminants in water bodies, while investigations into the occurrence of these drugs in the aquatic environment could serve as an indicator for adjustments to these regulations. Consequently, it is essential for government authorities to prioritize the review of environmental legislation, fostering scientific research on these compounds and expanding the available data concerning the occurrence of antibiotics in aquatic matrices within the country.

Despite the absence of specific regulations regarding antibiotics in Brazilian water bodies, it is imperative to acknowledge that certain recent decrees may have an indirect impact on the occurrence of pharmaceuticals in water matrices.

The first one, Resolution No. 44, 26th October 2010, created and implemented a restrictive law on over-the-counter sales of antimicrobial, in November 2010.[91] After this law, there was a drop in the sales, higher in regions with better socio-economic conditions. However, this drop was then followed by an increase in sales even at a lower rate less than a year after the law was implemented.[10] For CIP and CFX, for example, between 2008 and 2010, prior to the law, the sales of these antibiotics saw a substantial increase of approximately 41.1 and 45.2%, respectively. However, following the implementation of the law, between 2010 and 2012, the growth in sales significantly declined to only 5.6% for CIP and 7.0% for CFX.[10]

The second one, the Decree No. 10.388, 5th June 2020,[92] established the reverse logistics system for expired or unused home pharmaceuticals for human use, industrialized or manipulated, and their packaging after disposal by consumers. With this law, some drugstores and pharmacies are set as fixed collection points and are obliged, at their own expense, to acquire, make available, and maintain, in their establishments, container dispensers, guaranteeing at least one fixed collection point where the population can discharge the expired or disused home medicines and their packaging.

However, the lack of monitoring and a comprehensive national database on the prevalence of antibiotics in aquatic matrices in Brazil makes it challenging to evaluate the actual effects of these decrees. In view of the above, it would be appropriate from the perspective of environment protection and public health, the establishment of a national legislation, monitoring list or guide values to monitor the concentration of pharmaceutical residues in aqueous environment.

6. Conclusions

Based on this review and taking into account the current situation of monitoring antibiotics in Brazilian waters, it is clear that several aspects have to be highlighted:

(*i*) Over the past twelve years, 23 antibiotics were monitored and detected in five aqueous matrices in the three most populous Brazilian regions.

(*ii*) Despite the urgent environmental and health concerns associated with this topic, the number of publications focused on monitoring antibiotics in Brazil remains limited, and the available data are insufficient to establish a comprehensive scenario for the entire country.

(*iii*) Further studies are required to evaluate the capacity of the different treatments for removing antibiotics in STPs.

(*iv*) Even with few data, Brazil showed to have one of the highest levels of antibiotic contamination in SW in the world. This is largely due to the limited coverage of sewage collection and treatment in the country, as well as the lack of effectiveness in the processes employed in STPs for the removal of these compounds.

(*v*) Although there are no specific regulations regarding antibiotics in Brazilian water bodies, recent decrees on sale and disposal of pharmaceuticals may have an indirect impact on the occurrence of these

pharmaceuticals in water matrices. However, the lack of monitoring and a comprehensive national database on the prevalence of antibiotics in aquatic matrices in Brazil makes it challenging to evaluate the actual effects of these decrees, highlighting the need for a national legislation and monitoring system.

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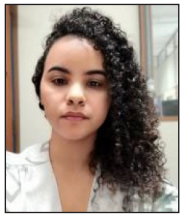

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