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Environmental risk caused by drug waste in the city of Rio de Janeiro, Brazil, during the SARS-Cov19 pandemic

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Abstract *The relationship between the distribution of medicines used in the Pandemic by SARS-COV-19 in the municipality of Rio de Janeiro and the estimated level of environmental risk caused by their residues was evaluated. The amount of medicines distributed by primary health care (PHC) units between 2019 and 2021 were collected. The risk quotient (RQ) corresponded to the ratio between the estimated predictive environmental concentration (PECest) obtained by the consumption and excretion of each drug and its non-effective predictive concentration (PNEC). Between 2019 and 2020, the PECest of azithromycin (AZI) and ivermectin (IVE) increased between 2019 and 2020, with a decrease in 2021 probably due to shortages. Dexchlorpheniramine (DEX) and fluoxetine (FLU) fell, returning to growth in 2021. While the PECest of diazepam (DIA) increased over these 3 years, ethinylestradiol (EE2) decreased possibly due to the prioritization of PHC in the treatment of COVID-19. The largest QR were from FLU, EE2 and AZI. The consumption pattern of these drugs did not reflect their environmental risk because the most consumed ones have low toxicity. It is worth noting that some data may be underestimated due to the incentive given during the pandemic to the consumption of certain groups of drugs.*

Key words *COVID-19, Environmental hazards, Pandemics, Pharmaceutical preparations, Toxicity*

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Introduction

Medication is extremely important when it comes to combating diseases and illnesses and provides a means for increasing the life expectancy of people. However, medication can also be the cause of health problems when used improperly or for purposes other than their therapeutic indication[1]. Inappropriate use of medication is the second largest cause of domestic poisoning in Brazil[2], which is the seventh largest consumer of medication in the world[3]. One of the reasons for these high consumption levels is the sale and marketing strategies used by manufacturers[4]. During the COVID-19 pandemic, the influence of the media, as well as government incentives, caused an increase in the consumption of various drug classes[5]. Poisoning by these substances may have increased during the pandemic owing to self-medication. However, there is little information on the possibility of residues from these drugs entering water systems and affecting the wild biota.

These residues reach the environment through incorrect disposal of surplus and/or expired medication and through their natural excretion after metabolization[6]. As such, even when consumed in full, drug residue can enter the drainage and sanitary sewage systems of cities, contaminating water sources[7]. Various authors have reported the presence of drug residues in water systems in almost all continents: Europe[8-10], North America[11], Asia [12,13], Oceania [14,15], and South America[16].

These compounds are called emerging contaminants, and there are no regulations regarding their environmental threats[17]. The effects can be observed in very low concentrations (ng/L) and in various aquatic species[18-23]. Among these, antimicrobial resistance caused by antibiotic residue in the environment and the effects from estrogen observed in fish owing to the presence of hormones are the most cited in the literature[24].

Studies have used the risk quotient (RQ) in the assessment of ecological risk for emerging contaminants[25,26]. It can be calculated using the quotient between the concentration found in water systems (predicted environmental concentration, PEC) and maximum concentration at which no effect is observed on a given aquatic organism (predicted no-effect concentration, PNEC). PNEC values are constantly being updated/reassessed to enhance the effectiveness of risk assessment[27]. Large RQ values show that the concentration of emerging contaminants in the environment exceed the ecological safety threshold (PNEC), thereby posing a threat to aquatic species[28]. When the PEC value is lower than that of the PNEC, the risk can be considered as insignificant (Table 1).

An indirect method of estimating the concentration values of a given drug in the water system (PEC*exc*) is based on its consumption. This method requires data on the degree of metabolization and excretion of a given drug, as well as the possibility of it being removed/degraded by the sewage treatment systems[29]. The city of Rio de Janeiro has an estimated population of over 6.5 million people[30], among whom 58% are served by primary health care (PHC) units[31]. Only 56% of the city's sewage is collected and treated[32], but most of the drug residue is not removed by conventional sewage treatment systems [18,33-35].

Our study assessed the estimated environmental risk from the residue of some drugs used during the COVID-19 pandemic, as a function of their distribution by PHC. For this purpose, we considered that all distributed drugs were properly used and that the pharmaceutical residue excreted through urine was placed in the sewage system without removal/degradation carried out by the sewage treatment systems.

Methodology

Study design

This exploratory study analyzed the medications distributed to the population of the city of Rio de Janeiro served by PHCs during the 2019-2021 period and the estimated risk of the residue from these drugs to the environment. This period is justified by the fact that a part of the drugs listed was used for managing the COVID-19 pandemic, declared in 2020.

Table 1. Risk exposure classification of aquatic biota with respect to pharmaceutical residue.

	Risk classification
RQ ≤ 0.1	Insignificant
0.1 < RQ ≤ 1	Low
1 < RQ ≤ 10	Moderate
RQ > 10	High

RQ: risk quotient; Source: environmentally classified pharmaceuticals, 2014.

Source: Authors.

Drug consumption

Data collection on medicines distributed to the population serviced by the public health system of the city of Rio de Janeiro between 2019 and 2021 using the SIGMA and SPPW/EXTRANET system, the use of which is restricted. For the purpose of this study, we assumed that all distributed drugs had been used properly. This collection was granted the consent of the agencies involved and the corresponding approvals from the relevant research ethics committees (ENSP 50881321.7.0000.5240 and SMSRJ 50881321.7.3001.5279). The drugs included in this study were azithromycin (antibiotic), ivermectin (antiparasitic), dexchlorpheniramine (antihistamine), diazepam (benzodiazepine), and fluoxetine (antidepressant), which have been widely used during the COVID-19 pandemic, as well as the 17α-Ethinylestradiol hormone, which is known as a drug with high potential risk and environmental hazard[36].

Estimation of drug excretion by the population

The excretion of each drug was determined of each drug using the pharmacokinetics of each product based on both the drug's package insert and other sources[37-42]. Only their unchanged excretion in the urine was considered, given the lack of data on their fecal excretion. Based on these values, we calculated the amount of drug excreted every day (QF*exc*) using equation 1.

$$QFexc = (Dose \times distributed\ QTDE)/365 \times \%exc \quad (1)$$

where *Dose* is the mass amount of the drug in each drug presentation; distributed QTDE is the amount of drug distributed to the serviced population per year; *%exc* is the percentage of drug that was eliminated exclusively in the urine after it was administered.

The volume of waste generated every day (Waste vol) by the population serviced by PHCs was calculated using equation 2.

$$Waste\ Vol = Total\ pop \times 0.58 \times Waste\ per\ capita \quad (2)$$

where *Total pop* is the estimated total population of Rio de Janeiro[30]; *0.58* corresponds to the population service by PHC[31]; *Waste per capita* is the amount of waste generated every day per person[43].

The concentration of drug excreted, or its estimated predicted environmental concentration (PEC*est*) in micrograms/liter (µg/L), by the population served by PHCs using equation 3.

$$PECest = QFexc/(Waste\ vol) \times 1{,}000 \quad (3)$$

Although 55% of the population of Rio de Janeiro has a collection and treatment system for generated waste, a decrease in the PEC*est* by virtue of it passing through sewage treatment processes was not considered, given the limited available information on the removal/degradation potential of these compounds in these processes.

Risk quotient

We calculated the potential risk (RQ) based on the PEC*est* and PNEC values of each drug, using Equation 4.

$$RQ = PECest/PNEC \quad (4)$$

PNEC values for freshwater aquatic organisms are available in the NORMAL (2022) ecotoxicology database. The RQ classification was based on Environmentally Classified Pharmaceuticals (2014) (Table 1).

Results and discussion

Consumption of medication

Graph 1 shows the medication amount consumed by the population serviced by PHCs per year. Diazepam consumption slightly increased in 2020 and 2021 compared with 2019. Meanwhile, ethinylestradiol consumption decreased slightly. Azithromycin and ivermectin consumption increased in 2020 and decreased in 2021. Meanwhile, consumption of dexchlorpheniramine and fluoxetine decreased in 2020 and increased in 2021.

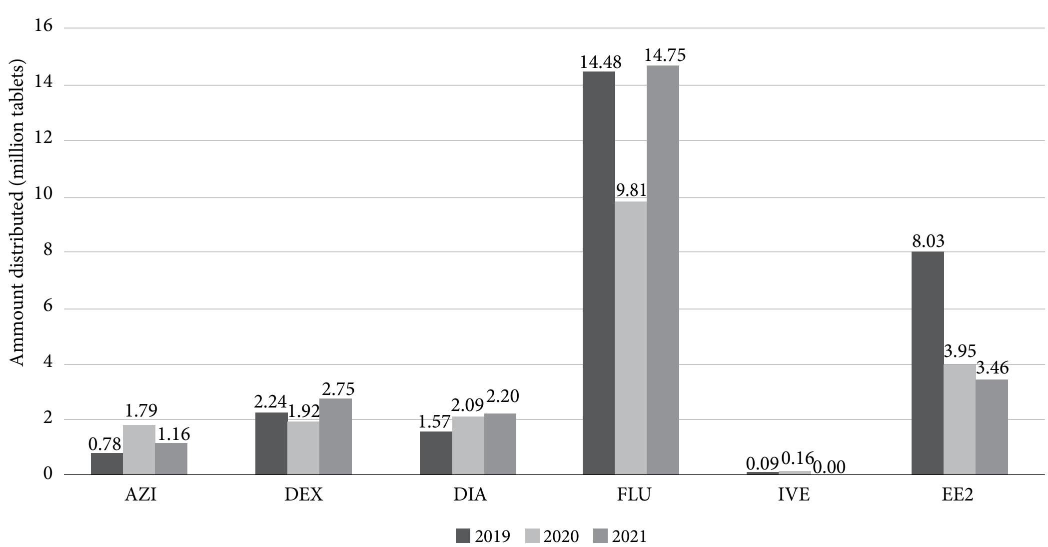
Diazepam was already a widely used medication for relieving tension and other somatic or psychological complaints associated with anxiety disorders. Given these characteristics, many people used it during the COVID-19 pandemic; therefore, diazepam use increased between 2019 and 2021[44,45]. Diazepam belongs to a class of drugs called benzodiazepines, which are indicated for the treatment of intense, disabling disorders or for extreme pain.

The drug levonorgestrel, which is associated with ethinylestradiol, is an oral contraceptive indicated for the prevention of pregnancy and control of menstrual irregularities. Its usage is tightly linked to public policies on birth control. A decrease in its consumption in 2020 and 2021 can be explained by the fact that health care units prioritized severe COVID-19 and severe-acute respiratory syndrome (SARS) cases[46]. Notably, there was no supply shortage during this period. Our study considered only the pharmacokinetics of 17α-ethinylestradiol, given that several studies have reported its harmful effects on wild aquatic biota [17,36,47,48], which would explain its low PNEC value (0.000035 μg/L). This drug was included in our study as a parameter for comparing its estimated environmental risk with respect to the other drugs[49].

Azithromycin was widely consumed during the COVID-19 pandemic owing to its properties. It has been recommended in the treatment of viral infections. Its anti-inflammatory effects could help decrease tissue damage caused by viruses, especially when administered at the beginning of the illness[50]. As such, this medication is part of the so-called COVID kit that was widely publicized by the Brazilian media, despite the fact that there is no scientific evidence regarding its effectiveness in the treatment of COVID-19[51].

Ivermectin is a drug used in the treatment of several kinds of parasite infestations, including intestinal strongyloidiasis, onchocerciasis, filariasis, scabies, and pediculosis[39]. During the COVID-19 pandemic, ivermectin was widely recommended by some health professionals for the prevention and treatment of COVID-19. Despite the absence of scientific evidence of its effectiveness for this use, broad speculations resulted in great demand for this drug by the population, which may explain the 76% increase in its consumption from 2019 to 2020 via PHCs. The increased demand for this drug caused a shortage in the network the following year (2021). According to The Human Data Science Company™ (IQVIA), along with the Brazilian Federal Pharmacy Council (CFF)[52], between 2019 and 2020, the consumption of ivermectin showed an increase of over 500%, which resulted in a market shortage. One of the problems with its high consumption is poisoning – ivermectin can cause liver damage and even lead to death.

Dexchlorpheniramine is a first-generation antihistamine indicated for the treatment of allergies, urticaria, pruritus, allergic rhinitis, insect bites, allergic conjunctivitis, atopic dermatitis, and allergic eczemas. Therefore, it was included in some protocols for the treatment of COVID-19[53]. Another factor that can explain the



Graph 1. Comparison of medication amount per year.

AZI = azithromycin; DEX = dexchlorpheniramine; DIA = diazepam; FLU = fluoxetine; IVE = ivermectin; EE2 = ethinylestradiol.

Source: Authors, based on collected data (2019-2021).

Ciência & Saúde Coletiva, 28(3):711-720, 2023

increase in its consumption between 2020 and 2021 was produced by the influenza outbreak that affected Rio de Janeiro[54].

Fluoxetine is the active ingredient of numerous psychotropic drugs; it acts as a selective serotonin reuptake inhibitor. This medication is administered for the treatment of depression, obsessive-compulsive disorder, anxiety disorder, and bulimia nervosa. This became one of the most widely prescribed drugs worldwide[55], including by public health systems. There was an increase in demand for this medication during the COVID-19 pandemic, which could explain its potential shortage in 2020. The use of psychotropic drugs is a concern for public health, since this medication is consumed by almost all age groups[56,57]. Health authorities should warn the population regarding the indiscriminate use of this drug class, making them aware of risks to health and quality of life, as well as of the adverse effects and impacts on the environment[5].

Excretion of medication and environmental risk

Considering the population served by PHCs (58%) in Rio de Janeiro, volume of generated wastewater per person (150 L/day), and pharmacokinetics of each drug, we calculated the concentration of each excreted drug (eqs. 1 and 2). For azithromycin, the main route of excretion is biliary excretion, but 6% of the drug is eliminated in the urine after its oral administration[42]. Dexchlorpheniramine and its metabolites are mainly excreted in the urine, with 19% of the dose appearing within 24 hours and a total of 34% within 48 hours[38]. Human metabolism of diazepam produces metabolites resulting from enzymatic biotransformation reactions that prolong the length of pharmaceutical activity. The main metabolites formed are nordiazepam, temazepam, and oxazepam; temazepam and oxazepam can also be used as anxiolytics in several countries[58]. These substances are excreted by conjugation with glucuronic acid along with quantities ranging from 5% to 50% of diazepam, unchanged in the urine[40].

The main metabolite of fluoxetine is norfluoxetine; the two have the same potency and selectivity. Approximately 80% of it is eliminated in the urine and 15% is excreted in the feces[41]. Ivermectin is metabolized in human liver microsomes and mainly excreted in the feces, with only 1% of it exiting in the urine[39]. Ethinylestradiol is primarily metabolized by aromatic hydroxylation, forming some metabolites and conjugates. Conjugated ethinylestradiol is excreted in the bile and subject to enterohepatic recirculation. About 40% of the drug is excreted in the urine, and 60%, through the feces[37]. Thus, we used the following excretion values: azithromycin, 6%; dexchlorpheniramine, 19%; diazepam, 50%; fluoxetine, 80%; ivermectin, 1%; and ethinylestradiol, 40%.

Table 2 shows the amount of each medication excreted daily in the urine (QF*exc*) and estimated concentration in the wastewater (PEC*est*). For comparison, we carried out a literature review regarding the PEC values for these six drugs[17,59-62].

The mean PEC values found in the literature for azithromycin, dexchlorpheniramine, diazepam, fluoxetine, ivermectin, and ethinylestradiol were 0.563, 0.025, $2.4.10^{-5}$, 0.54, 0.2, and 0.07 μg/L, respectively. Among the PEC*est* values obtained from the medication distribution/consumption data in Rio de Janeiro, only those for diazepam and fluoxetine exceeded the reference values. This result shows that mental health medications were the most consumed medication in Rio de Janeiro, probably owing to the social problems the city has faced over the years[44,57,63] that may have worsened during the pandemic. Although lower, the PEC for azithromycin in 2020 reached almost 50% of the PEC value found in the literature; this reflects its higher consumption as part of the treatment of the COVID-19 pandemic. Based on excretion (PEC*est*) and PNEC data for each drug, we could calculate the RQ (Table 3).

Ivermectin, dexchlorpheniramine, and diazepam presented an insignificant estimated risk during the analyzed period. However, the assessed levels could have been underestimated. The reason for this is that our study was carried out using only distribution data from PHCs and, according to data from the CFF (2021), in the 2019-2020 period, there was a shortage of this drug owing to high demand from other networks (private and hospital). As for diazepam, although it had a very high PEC*est* with respect to the values cited in the literature, its environmental risk was also negligible. Ivermectin could result in increased growth of animals receiving overdoses[64], whereas diazepam could cause changes in the behavior of fish exposed to its residue[59].

Azithromycin presented low risk in 2019 and reached moderate risk in 2020. This result reflects its use as one of the medications recommended by the health system ("COVID kits") for treatment during the COVID-19 pandemic. Despite decreased risk in 2021 (low risk), a potential shortage in the public network cannot be ruled

Table 2. Amount excreted and concentration by medication from 2019 to 2021.

Medicamento	2019		2020		2021	
	Amount excreted per day (mg/day)	Estimated excretion concentration (µg/liter)	Amount excreted per day (mg/day)	Estimated excretion concentration (µg/liter)	Amount excreted per day (mg/day)	Estimated excretion concentration (µg/liter)
Azithromicin	64,324	0,1091	146,808	0.2490	95,151	0.1614
Dexchlorpheniramine	2,330	0,040	1,996	0.0034	2.863	0.0049
Diazepan	10,720	0,0182	14,289	0.0242	15,085	0.0256
Fluoxetine	634,837	1,0770	429,998	0.7295	646,557	1.0968
Ivermectin	15	0,0000	26	0.0000	0	0.0000
Ethinylestradiol	264	0,0004	130	0.0002	114	0.0002

Source: Authors, based on collected data (2019-2021).

Table 3. Comparison of risk quotient (RQ) estimated between 2019 and 2021.

Medicamento	QR estimado 2019 (risco)	QR estimado 2020 (risco)	QR estimado 2021 (risco)
Azitromicina 500mg	0.6326 (low)	1.4438 (moderate)	0.9357 (low)
Dexclorfeniramina 2mg	0.0120 (insignificant)	0.0102 (insignificant)	0.0147 (insignificant)
Diazepam 5mg	0.0314 (insignificant)	0.0419 (insignificant)	0.0442 (insignificant)
Fluoxetina 20mg	10.7696 (high)	7.2946 (moderate)	10.9684 (high)
Ivermectina 6mg	0.0002 (insignificant)	0.0003 (insignificant)	0 (insignificant)
Etinilestradiol 0,03mg	12.8006 (high)	6.3015 (moderate)	5.5060 (moderate)

Source: Authors, based on collected data (2019-2021).

out[65]. Meanwhile, this result can also be tied to the beginning of the vaccination campaign, especially for the most vulnerable age groups. A worrying fact about the risk associated with azithromycin is the potential for the development and proliferation of antibiotic-resistant bacteria[60].

Fluoxetine showed a high environmental risk with similar values in 2019 and 2021. Even if the risk in 2020 was moderate, its value was close to the moderate–high limit, which might be related to shortages. Fluoxetine and its metabolites are toxic for the environment, scoring 6, on a scale from 0 to 9, in the PBT (persistent, bioaccumulative, and toxic) index[55,66]. The presence of fluoxetine in the environment can interfere with the development and behavior of aquatic animals[67].

Ethinylestradiol presented a high estimated risk only in 2019. In 2020 and 2021, the PHC units were dedicated to providing priority care to SARS patients[46], and the distribution of birth control medication, which includes ethinylestradiol, was reduced. This could be associated with the moderate environmental risk level observed in this period (Table 3). In addition to causing nuclear abnormalities in aquatic organisms, ethinylestradiol in the environment can interfere with the reproductive system and deviate the sex ratio in a species[68].

Even if drug distribution is directly related to increased exposure to the environment, the estimated environmental risk (RQ) will depend on the toxicity of the drug and its metabolites. Although some medications were consumed more, this was not reflected in the significance of their risk. Medications that have greater environmental toxicity increased or remained at the same estimated environmental risk. Given the importance of the subject, further research must be conducted on the environmental impact of drugs, especially those used for mental health, as they were consumed more during the period studied. Additionally, the residue from various drugs must be monitored in water sources to obtain PEC values within Brazilian local realities; this would allow for a better understanding of the relation between consumption and excretion/disposal of residues in the environment.

Conclusion

The environmental risk of azithromycin increased in 2020, which can be attributed to increased consumption linked with its use in the treatment of COVID-19. This trend regarding risk was not observed in the drug ivermectin, given that there was a shortage of it. The estimated environmental risk caused by fluoxetine was constant (high), with a slight decrease in 2020, probably owing to a shortage during the pandemic. ethinylestradiol was the only medication whose risk was significantly reduced in the 2020–2021 period, given the logistics of care provided by PHCs.

The primary research results that were used in the preparation of this article were inserted in the Scielo.Data repository: https://doi.org/10.48331/scielodata.QZOVID

Collaborations

CPFA Souza: conception and design of the article, analysis and interpretation of data and writing of the article. DC Kligerman: article writing, critical review, approval of the version to be published. JLM Oliveira: article writing, critical review, approval of the version to be published. GM Bezerra: analysis and interpretation of data and writing of the article.

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