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POINTS OF REFERENCE

Points of Reference are part of a regular series intended to address an emerging or controversial topics of interest to the scientific community.

COVID-19 Therapies in Brazil: Should We Be Concerned with the Impacts on Aquatic Wildlife?

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Brazil is currently the Latin American epicenter of the coronavirus disease 2019 (COVID-19) pandemic, whose impacts have permeated the economic, social, and healthcare spheres. Amid its worst health crisis, the country has also been struggling with antiscience political narratives that promote the widespread use of chloroquine, hydroxychloroquine, and, more recently, the antiparasitic ivermectin. As a result, an increased demand for these pharmaceuticals has been observed across the country, with a sales increase of >50% in comparison to 2019 (Conselho Federal de Farmácia 2020).

This steep increase in the use of such drugs, however, may pose risks to Brazil's highly biodiverse biomes—an issue that overlaps with the country's precarious wastewater-treatment situation. Data from 2018 indicated that almost half of the Brazilian population does not have access to sewage collection; the northern and northeast regions (historically at economic disadvantage) are particularly vulnerable because only 10.49 and 28.01%, respectively, of their inhabitants have access to adequate sanitation (Figure 1). Nationwide, 46% of collected sewage is treated, but high treatment rates (>80%) are observed in only 21 of the 100 largest cities (Instituto Trata Brasil 2018). Such poor sanitation conditions have detrimental effects on human health and the environment.

Many contemporary pollutants are pharmaceuticals, which is concerning because of their toxicity to aquatic organisms, ever increasing amounts, and relative chemical stability. Organ damage, reproductive toxicity, hormonal disruption, behavioral changes, mutagenicity, and carcinogenicity are some of the reported effects of widely used drugs on various amphibian, fish, and invertebrate species (Organisation for Economic Co-operation and Development 2019). In Brazil, pharmaceuticals are particularly important as emerging pollutants because of self-medication, inappropriate disposal of unused or expired medications in the toilet or common garbage, and the lack of efficient wastewater collection/treatment to remove chemical wastes, as well as lack of regulations establishing environmentally acceptable concentrations (Quadra et al. 2017).

A wide variety of pharmaceuticals for human or veterinary use (e.g., analgesics and anti-inflammatories, antibiotics, hormones, caffeine) and personal care products (triclosan) have already been found in Brazilian water bodies (mainly rivers, reservoirs, and potable water; Quadra et al. 2017). These water samples, mostly obtained from the southeast region of Brazil, indicate the looming threats of these compounds because this region has the largest rate of sewage collection and treatment (Figure 1). Thus, with a massive increase in the use of chloroquine, hydroxychloroquine, and ivermectin in Brazil and their likely entry into aquatic environments, what can we expect from the effects of these drugs and their metabolites on aquatic wildlife?

Ivermectin is a macrocyclic lactone used worldwide to treat human and animal parasites such as scabies and ticks since the 1980s, and its environmental effects are better understood than those of chloroquine and hydroxychloroquine. Environmental fate studies on ivermectin have shown that this hydrophobic compound may persist in soil and sediment as well as accumulate in various aquatic organisms, leading to various degrees of toxicity, with larval instars of invertebrates being particularly vulnerable (Mesa et al. 2017).

In turn, chloroquine and hydroxychloroquine are aminoquinoline drugs widely used in the prevention and treatment of malaria despite the gradual reduction of their use in regions with reported resistant *Plasmodium* strains. Also, hydroxychloroquine is used to treat rheumatoid arthritis and systemic

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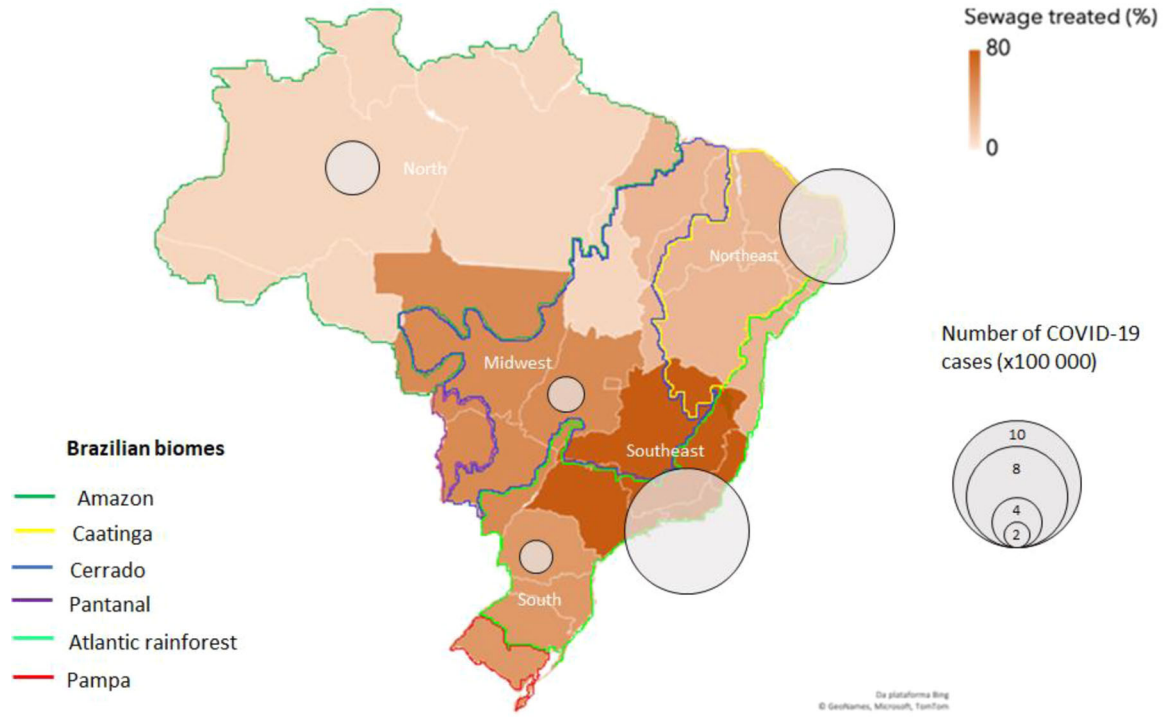

FIGURE 1: Treated sewage and predominant biomes across Brazilian regions. Bubble sizes represent the number of confirmed COVID-19 cases (×100 000) registered until 6 August 2020 (Center for Systems Science and Engineering at Johns Hopkins University 2020).

lupus erythematosus. Despite the limited data on chloroquine toxicity to aquatic wildlife, Zurita et al. (2005) were able to classify this compound as "R52/53 Harmful to aquatic organisms and may cause long-term adverse effects in the aquatic environment." Data on the environmental effects of hydroxychloroquine are even more scarce; the available information tagged this compound as an insignificant environmental risk in the prepandemic scenario despite its persistence (Health and Medical Care Administration–Region Stockholm 2020).

In Brazil, efforts to identify and mitigate the effects of these drugs on ecosystems are compromised because of the absence of a robust regulatory framework for emerging contaminants. The current legislation sets limits for some herbicides and agricultural products in surface waters but largely ignores pharmaceuticals. In the absence of regulations to establish monitoring practices or maximum contaminant levels for these drugs in the environment, many uncertainties about the potential short- and long-term impacts of these drugs on ecosystems remain.

Fragile Brazilian biomes, such as the Amazon (northern region), Caatinga and coastal region of the northeast, and the Atlantic rainforest (southeast region) are of particular concern given the high incidence of COVID-19 cases in these areas (Center for Systems Science and Engineering at Johns Hopkins University 2020; Figure 1). The large-scale use of unproven drugs in response to the pandemic may add undue weight to the increased volume of pharmaceuticals entering the environment, leaving the local biota vulnerable to the harmful effects of these contaminants. The north (Amazonas and Pará), northeast (Bahia, Ceará, and Maranhão), and southeast (Rio de Janeiro and São Paulo) regions, which are completely inserted in these biomes, have registered approximately 1 500 000 COVID-19 cases (Center for Systems Science and Engineering at Johns Hopkins University 2020)—more than half of all nationwide cases.

A nationwide coordinated response is urgently needed to monitor the levels and investigate the impacts of these emerging contaminants. First, investigating their levels in sewage systems is necessary to assess the extent of the contamination with the parental compounds and their metabolites. Toxicity tests with bioindicator species can help to evaluate the potential risks to aquatic environments. Particularly relevant topics include long-term toxicity, bioaccumulation, and the synergistic effects with other common (non-) pharmaceutical pollutants. Cooperation across research institutes and governmental agencies, especially in the most affected areas, would help to assess the hazard based on environmentally relevant concentrations.

Disclaimer—All authors have no interest to declare. The views expressed in the present review are solely those of the authors.

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Data Availability Statement—All data and information presented were accessed from websites with free access and from the specialized scientific literature as described in the references. Data, associated metadata, and calculation tools are also available from the corresponding author (davi@dbm.ufpb.br).

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