

Review

One Health, Antimicrobial Resistance Genes and Two Important Associated Human Activities in Brazil: Coastal Tourism and Agriculture/Livestock Farms

Marcos Alaniz Rodrigues^{1,2,3}, Ana Júlia Reis^{1,2}, Alex Sandra Avila Minasi¹, Ana Paula Furtado Carneiro da Fontoura¹, Dienefer Venske Bierhals^{1,2}, Livia da Silva Freitas¹, Mariana Quaresma Souza^{1,2}, Rodolfo Moreira Baptista^{1,3}, Flávio Manoel Rodrigues da Silva Júnior¹, Pedro Eduardo Almeida da Silva^{1,2,3}, Daniela Fernandes Ramos^{1,2,3*}

¹ Postgraduate in Health Science (PPGCS), Federal University of Rio Grande (FURG), Rio Grande, RS, Brazil.

² Research Group in Medical Microbiology (NUPEMM), Federal University of Rio Grande (FURG), Rio Grande, RS, Brazil.

³ New Drugs Development Group (NUDEFA), Federal University of Rio Grande (FURG), Rio Grande, RS, Brazil.

Received September 26, 2024; Accept May 20, 2025

Abstract

Human activities are a reflection of the evolution of tools and development of technologies. With that also comes the drawback of these activities affecting native animal and plant populations, along with the broader ecosystem impact that all living beings on the planet are vulnerable to. The generation of antimicrobial resistance genes is one of these results, and this review aims to track two approaches related to antimicrobial resistance development, directly or indirectly associated with human economic activities, representing some of the most profitable businesses in Brazil: coastal tourism and agriculture/livestock. These activities represent a large part of the investment from governments in Brazil and the consequences of the misuse can be potentially harmful and are not completely understood. The recent increase in the number of infections caused by resistant microorganisms is of paramount importance and is generating concern all over the world. This review is in line with the One Health approach.

Keywords: Agriculture, Antimicrobials, Antimicrobial Resistance Genes, Coastal Tourism.

INTRODUCTION

There is growing evidence that disturbances caused by anthropogenic activities are shifting the already delicate balance between a healthy and a sick environment. Sick environments refers to the degradation of habitats, leading to adverse effects on the biota present, and this degradation stems from factors such as pollution, habitat destruction and climate change (Smale *et al.*, 2019). Byproducts like pollutants, metals and others that come at the cost of the advances of modern medicine and technology, are at the center of an almost insoluble problem that needs to be addressed: the evolution of resistance forms of microorganisms like bacteria, fungi and viruses.

Antimicrobial resistant (AMR) bacteria are a major concern for both human health and the environment, and the indiscriminate use of antimicrobial compounds is increasing the number of deaths, days of hospitalization as well as hospital expenses (Komijani *et al.*, 2021). An estimated 1,4 million deaths worldwide were associated with bacterial antibiotic resistance in 2019 (Murray *et al.*, 2022; Naghavi, Mohsen *et al.* 2024), and by 2050 up to 3,8% of all global domestic gross product could be lost due to AMR, with an economic loss of around 10 trillion dollars (World Bank, 2017). Antimicrobial resistance could also become the main cause of death in the world, with about 10 million deaths per year, which is more lethal than prostate and breast

*Corresponding author: daniferamos@gmail.com

cancer together (Serwecinska, 2020; WHO, 2022). The One Health concept comprises the connection and interrelation of human, environmental and animal health, and this approach is also very present in debates on AMR where it is possible to develop effective public policies in the prevention and control of diseases at the regional, national and global levels (Van Bruggen *et al.*, 2019; WHO, 2018).

Since their discovery, antimicrobials have been at the forefront of pharmacological strategies for treating infectious diseases. Evidence began to emerge in the late 19th century with the introduction of the term “antibiotic,” referring to substances that exert harmful effects on living organisms, particularly microorganisms. This concept gained prominence during the golden era of antibiotic discovery and was later refined by Selman A. Waksman in 1947. Waksman defined antibiotics as chemical compounds produced by microorganisms capable of inhibiting the growth and inducing the death of other microorganisms, particularly bacteria. This definition was further expanded by incorporating synthetic chemistry approaches, as proposed by Paul Ehrlich in 1910. (Halawa *et al.*, 2024). Certainly, the discovery of these therapeutic agents has significantly contributed to the reduction in mortality rates, particularly during World War II, and their application subsequently expanded beyond therapeutic use to include non-therapeutic purposes, such as growth promotion in livestock and agriculture on a global scale (Cycon *et al.*, 2019). However, considering that most bioactive compounds targeting microorganisms originate from nature itself and that the environment has been inundated with bioactive molecules in various contexts—such as the use of pesticides, biocides, and even personal hygiene products—antimicrobial resistance has emerged almost simultaneously. This phenomenon is driven by the continuous selective pressure exerted on microbial populations, promoting their survival and adaptation in response to this persistent biochemical assault on the biosphere (Davies, 2006).

From an evolutionary perspective, a sequence of events appears to drive the transfer of resistance genes and the emergence of new resistance mechanisms and resistant microorganisms. Additionally, these processes can promote cross-resistance between antimicrobials and other compounds, such as metals, pharmaceuticals, and Personal Care Products. These cyclic events typically begin with the exposure of an environment or microenvironment to selective pressure, leading to the selection of resistant microorganisms. Over time, these microorganisms persist due to the presence of genes capable of mobilization within the genome, such as insertion sequences. These genes can be relocated and transferred between cells through plasmids, integrative

conjugative elements, or even via horizontal gene transfer, including mobilized genes carried by bacteriophages (Larsson & Flach, 2022).

In this sense, antimicrobials are one of the first compounds that come to mind regarding AMR, as allies in the fight against infectious diseases, but mainly in their indiscriminate use and irrational disposal (WHO 2015; 2018). Despite that, there are other compounds that play a major role in the evolution of novel and complex processes of AMR evolution, that are not in the center of actions of AMR monitoring (Serwecinska, 2020).

It is currently known that antimicrobials can reach different environmental compartments, but there is still a need to elucidate all possible sources of antimicrobial resistance genes (ARG) related to these drugs, and how these genes can persist, in terms of transmission between different organisms when they reach the environment. Antimicrobials can also inhibit the growth of other organisms like plants, fungi and algae, and therefore it is one of our generation's challenges to determine the fate and action of these drugs in the wild (Larsson *et al.*, 2007; Da Silva *et al.*, 2022; Cycon *et al.*, 2019). There is a growing body of evidence that Pharmaceuticals and Personal Care Products can be also a source of emerging contaminants, and the effects of exposure to this group of chemical contaminants on non-target organisms are still a source of concern with poor information (Da Silva *et al.*, 2022).

Various interconnected human, animal, and environmental habitats can contribute to the emergence, evolution, and spread of resistance, whether through contamination by resistant microorganisms (microbiome) or antimicrobial resistance genes (resistome). The health of these environments, within the framework of the One Health approach, represents one of the most significant public health challenges of today (Hernando-Amado *et al.*, 2019). The increasing selective pressures caused by the excessive use of antimicrobials in hospital and healthcare settings, their application in the prevention and growth promotion of domestic and farm animals, and the inability to effectively remove them in wastewater treatment plants contribute to the accumulation of these compounds and antimicrobial resistance genes. This, in turn, perpetuates the cycle of emergence, evolution, and persistence of resistomes and microbiomes driven by anthropogenic activity. (Zhuang *et al.*, 2021).

Antimicrobials are complex molecules that act in different ways and have different chemical structures and classes. They are widely prescribed for the treatment of diseases in humans and animals, and also in contexts of food production and prevention of disease spread. Most of these compounds are not completely metabolized in the body of humans and animals, and a large amount is discharged into water and soil by disposal of sewage,

animal feces, sludge and bioflocs from Waterworks that are used as fertilizers (Serwecinska, 2020). Residues from the food and pharmaceutical industries, from hospital and domestic effluents and from the treatment of animals in agriculture are among the main sources of the contamination by antimicrobials and other compounds like metals and pesticides (Ejaz *et al.*, 2022).

The increase of the AMR bacteria and the rapid dissemination of ARGs is considered an alarming global issue (WHO, 2022). A recent review by Zhuang *et al.* (2021) highlights the main types of ARGs identified across six continents, as well as the primary antibiotic families associated with these findings. Notably, β -lactam resistance genes, particularly bla (CTX-M, NDM, TEM, OXA, CPC, etc.), are among the most frequently reported. Additionally, glycopeptide resistance genes, such as mecA, have been identified in over a thousand publications and are strongly associated with multidrug resistance phenotypes. Moreover, similar to global trends in antibiotic consumption, Asia stands out in publications reporting the presence of resistance genes across various environmental compartments. In contrast, the Americas rank among the regions with the lowest number of scientific publications on this subject (Zhuang *et al.*, 2021; Bobate *et al.*, 2023).

Tourism is indirectly linked, and agriculture is directly related to changes in the environment. These activities represent an important part of the investment from governments in Brazil and the consequences of the misuse can be potentially dangerous and are not completely understood in the One Health concept.

Considering the environmental niches of these resistomes, healthcare settings such as hospitals and animal farming environments, including aquaculture and agriculture, have gained significant attention. Despite being distinct in terms of antimicrobial usage patterns, these environments serve as key hotspots for the presence and dissemination of different antimicrobial classes and, consequently, resistance genes (Zhuang *et al.*, 2021). On the other hand, globally, studies assessing the presence of other contaminants that may exert environmental selective pressure and contribute to the emergence of new resistomes and microbiomes in air, water, and soil remain scarce. Furthermore, many investigations overlook the indirect anthropogenic impact these reservoirs could have on human health and animal farming, such as in aquaculture.

In this article, two approaches related to antimicrobial resistance development, directly or indirectly associated with human economic activities, representing some of the most profitable are presented: coastal tourism and agriculture/livestock.

Coastal Tourism and Antimicrobial Resistance Genes

Tourism is one of the most profitable activities in the world. The world gross domestic product of this economic activity was around 4% in 2019. In Brazil, the touristic activity promotes economic development in several places such as coastal and marine areas, especially on beaches in seasons with high temperatures. Such activity is also driven by various means of transport. Cruises, for example, transported more than 30 million passengers in 2019. In this context, people are starting to visit coastal regions as a leisure and wellness activity (WTTC, 2019; SRD, 2019).

Brazil has a coastline of approximately 8,000 km, made up of beaches and attractive landscapes, with a high tourist appeal. Due to this geographic feature, its contribution reached more than 100 billion of the Gross Domestic Product (GDP) in 2019 and favored the increase in population density in coastal regions over the last few decades, resulting in a strong urbanization process and increase of the access to these regions (WTTC, 2019; IBGE, 2011; Cruz, 2018).

There are evident impacts in the misuse of coastal areas, and the overpopulation of beaches during vacation and summer seasons. One of these impacts is related to the higher volume of pollutants and other contaminants, such as sewage water and the transport of different species of bacteria whose interactions with the environment are vast and still unknown (Zhang *et al.*, 2017; Araújo, 2016) (Figure 1). Its effects comprise changes in fauna and flora, climate, temperature and health damage, among others, including natural disasters (Chen *et al.*, 2019; Furlan *et al.*, 2020; Gaeta, 2022; IPCC, 2022).

Health issues are at the forefront of studies evaluating genes associated with antimicrobial resistance, particularly in relation to contaminants in Brazilian coastal water bodies (Araújo, 2016; Pereira *et al.*, 2019; Jang *et al.*, 2021). Polluted coastal waters, contaminated by fecal matter from urban or agricultural runoff, wastewater treatment plant discharges, wild animal excrement, or rainwater, can pose significant risks to exposed individuals engaging in tourism or aquatic sports. These conditions facilitate the translocation of bacteria and resistance genes, further contributing to the spread of antimicrobial resistance (Leonard *et al.*, 2015).

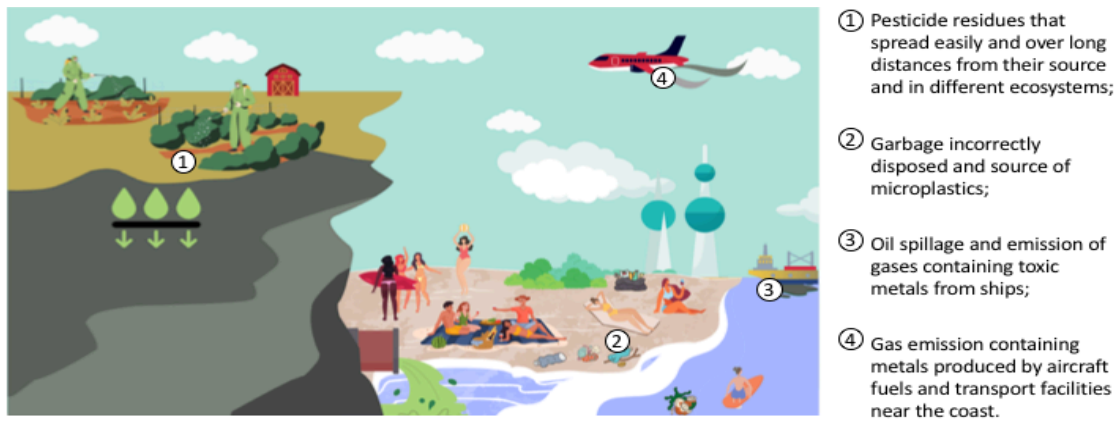


Figure 1. Sources of pollutants from coastal regions, possible of driving selection of ARGs.

In Brazil, the primary sources of antibiotics in aquatic environments include wastewater discharge, waste disposal, and the impacts of aquaculture (De Araújo & Do Nascimento, 2014; Lima *et al.*, 2023). These factors not only contribute to the rise of antimicrobial resistance but also lead to significant economic losses in the sector. Studies assessing antimicrobial resistance in aquaculture have shown that 90% of bacterial isolates from aquatic organism farming exhibit resistance, with 20% displaying a multidrug-resistant phenotype (Lin *et al.*, 2015; Pepi & Focardi, 2021).

Researchers assessed a coastal lagoon in southern Brazil during both peak and off-peak seasons. Even during periods of intensified anthropogenic activity, antibiotic residues were either undetected or remained below the minimum detection limit ($400 \text{ ng}\cdot\text{L}^{-1}$). However, resistant bacteria carrying β -lactam resistance genes and efflux pump systems were present in samples from both seasons. This suggests that even low antibiotic concentrations may have contributed to the selection of resistance in susceptible wild-type populations (Leite *et al.*, 2019). Additionally, water and sand samples collected in February 2019 from various urban beaches in two southeastern Brazilian states revealed the presence of genes encoding resistance to polymyxins, β -lactams, fluoroquinolones, aminoglycosides, tetracyclines, glycopeptides, and other antibiotic classes. Notably, the *mcr-9*, *bla-KPC*, and *cftr* genes were detected, frequently associated with multidrug resistance in both Gram-positive and Gram-negative bacteria. Moreover, high levels of fecal coliforms were also observed, further indicating significant contamination in these coastal environments (Furlan *et al.*, 2020; Rueda *et al.*, 2021).

In the northern region of Brazil, diarrheagenic *Escherichia coli* strains originating from fecal contamination were identified in water samples from one of the main beaches in Tocantins. These strains exhibited resistance to sulfamethoxazole-trimethoprim, tetracycline, ampicillin, and chloramphenicol, highlighting concerns about water quality and potential public health risks in the region (Oliveira *et al.*, 2012). The authors suggest that the

scarcity of wastewater treatment plants in the study region may have contributed to the translocation of these strains and the emergence of resistant isolates. Consequently, the lack of studies in the northern and central-western regions of Brazil appears to be linked to lower population density, whereas the higher concentration of agro-industrial activities and more developed sanitation infrastructure in the southern and southeastern regions have resulted in greater research focus in those areas (Oliveira *et al.*, 2012).

Another important factor in water contamination is its direct relationship with environmental pollution driven by population growth. Anthropogenic impacts significantly affect lakes, rivers, and coastal ecosystems through contamination by sewage and chemical compounds such as pesticides, hormones, and antibiotics, which are widely used in both human and veterinary medicine (Salloto *et al.*, 2012).

Several factors can increase health risks in recreational coastal waters, including: the enhancement of selective pressure on environmental bacteria, leading to the expression of resistance genes and bacterial virulence mechanisms; an increased rate of genetic transfer between bacteria, particularly those colonizing the gastrointestinal tract; and the persistence of these resistant microorganisms even in the absence of selective pressure (Leonard *et al.* 2015). The risk of infections by resistant microorganisms is increased by contact of the local population with contaminated water, and also by the ability of some bacteria to develop biofilm, which is an important reservoir of ARG (Abe *et al.*, 2020). Besides that, people exposed to coastal waters present an increase in the diversity of microorganisms and resistance genes in their skin (Nielsen *et al.*, 2021). In this context, surfers and sailors may be four times more susceptible to infections by resistant microorganisms (Leonard *et al.*, 2018).

Another major concern regarding antimicrobial resistance (AMR) and the impacts of coastal tourism is plastic contamination. Plastics account for 88% of all waste collected on beaches and originate from various

sources, including tourism-related activities and improper disposal by fishing vessels and cargo ships in coastal regions (UNEP, 2016; UNEP, 2018; Garcés-Ordoñez *et al.*, 2020), and can be classified as macroplastic (>25 mm) and microplastic (0.1 µm-5 mm) (Alimi *et al.*, 2018). The presence of plastic materials in coastal areas can also have negative impacts on biodiversity, such as animal welfare (ingestion, suffocation, etc.), biodiversity, seafood safety, navigation and human health (GESAMP, 2019). Plastics can also serve as a substrate and colonize marine animals, algae and microorganisms, as found in sediments and waters samples collected in coastal region in Brazil (Lacerda *et al.*, 2020; Neto *et al.*, 2019). The excessive accumulation of plastics in aquatic environments, combined with their interaction with microorganisms, is referred to as the plastisphere (Lacerda *et al.*, 2020). However, its role in the production and dissemination of antimicrobial resistance genes (ARGs) remains not fully elucidated.

A study conducted in a bay along the Brazilian coastline found that a significant portion of the plastic forming the plastisphere in benthic regions—77%—consists of fragments from objects used in fishing practices. These fragments facilitate the development of pathogenic fungi and bacteria, which use microplastics as vectors due to their light weight and resistance to degradation (Kirstein *et al.*, 2016; Viršek *et al.*, 2017; Neto *et al.*, 2019).

Studies involving the plastisphere have revealed a directly proportional relationship between the variety of antimicrobial resistance genes (ARGs) and the quantity of plastics. As the amount of plastic increases, so does the diversity of ARGs, suggesting that plastic contamination can contribute to the spread of antimicrobial resistance in aquatic environments. Polymers such as polyethylene (PE) showed a greater potential for inducing ARGs in estuarine waters. Distinct communities of bacteria that colonize microplastics in the aquatic environment are considered as a new microbial niche (Flach *et al.*, 2017; Lu *et al.*, 2019; Zhang *et al.*, 2020). Another study conducted with water used for mariculture detected a 15% higher presence of ARGs in microplastics formed by polyethylene terephthalate (PET) compared to findings in water samples. This indicates a tendency for ARG production by microorganisms in the plastisphere (Zhang *et al.*, 2020).

Trace metals in the soil near rivers in mining activity regions are also related to the emergence of ARGs. Cadmium and mercury are two examples found in mining that instigate the production of ARGs in Actinobacteria and Proteobacteria. Furthermore, metals at lower concentrations are capable of facilitating the transfer of these genes between microorganisms (Ji *et al.*, 2012; Yan *et al.*, 2020).

There are evident impacts that cruise ships, oil tankers, cargo and fishing ships that transit close to tourist regions have on the environment, and some authors showed robust evidence of these impacts in spilled waste. In Brazil, a large spill in the northeast region contaminated several tourist beaches, interfering with local biodiversity, the fish market and the health of people that reside in this region. The spill was considered one of the largest in the world, which triggered several discussions about methods to reduce the concentration of this pollutant in the environment (Soares *et al.*, 2022).

These pollutants are capable of causing increased expression of ARGs in a wide variety of bacterial species (Chen *et al.*, 2020). Oil spills are extremely destructive events, causing changes in autotrophic communities, due to macrofaunal and microorganism alteration associated with primary production in these locations (Lee & Lin, 2013). There are still questions to be answered about these pollutants and their possible interactions with microorganisms, since the sources of contamination and the variety of pollutants in water are diverse. However, the influence on the selection and resistance of microorganisms in the environment, the risks to the environment and human activities, which are known to be the main forces for the insertion of pollutants in the world, are evident, although the true impact in human and animal health still unknown (Martinez, 2009).

Agriculture/Livestock Farming and Antimicrobial Resistance

Brazil is a country that stands out in the world agricultural scenario. The country's rise in the agricultural sector began mainly in the 1990s as a result, in part, of government investments in policies aimed to ensure food security for the population. Currently, it is estimated that about 30% of the Brazilian territory is used for agriculture (EMBRAPA, 2018). In 2021, sugarcane was the most produced agricultural product in the country, while in livestock the cultivation of chickens had the greatest prominence (IBGE, 2022).

Antibiotic consumption profiles in developing countries are influenced by indiscriminate use, particularly on large-scale farms where antibiotics are used not only therapeutically but also as growth promoters to increase productivity and meet the demand for animal-derived products. This practice inevitably leads to antimicrobial resistance as a consequence. Additionally, contamination of animal products, such as meat and milk, due to inadequate hygiene and handling conditions, along with the expression of virulence factors like biofilms on surfaces, promotes the persistence of various pathogenic bacterial species. In this context, poultry have been reported as potential carriers of

bacterial contamination, including those that produce antibiotic-degrading enzymes such as Extended-Spectrum β -Lactamases (ESBLs) (Manyi-Loh *et al.*, 2018).

Brazil is one of the largest producers of animal protein in the world, and as such, antimicrobial resistance has become a significant issue, particularly in pig and poultry farming. In the southern region of the country, where extensive cattle farming is practiced, there has been a marked reduction in the use of prophylactic and therapeutic antimicrobials, which has resulted in a somewhat lower impact on antimicrobial resistance compared to poultry and pig farming. It is important to note that most national studies focus on states or regions with high concentrations of animal production and animal products, such as dairy, particularly in the southern and southeastern regions (Rabello *et al.*, 2020).

Furthermore, many antimicrobial agents used in the treatment of animals on farms, despite being veterinary products, belong to the same pharmacological classes (such as cephalosporins and fluoroquinolones) as those used in humans. This similarity can promote cross-resistance mechanisms, as observed in studies conducted in regions with the highest agricultural production in southern Brazil (Rabello *et al.*, 2020; Brisola *et al.*, 2019; Nobrega *et al.*, 2021). In these studies, antimicrobial resistance genes (ARGs) were found in isolates from animal feces, mastitis infections, as well as in water and soil samples. These isolates also exhibited multidrug resistance profiles through the identification of ESBL and *qnr* genes, which confer resistance to β -lactams.

Animal farming operations, along with hospital effluents, have therefore been identified as primary sources of ARGs and antimicrobial accumulation. The high volume of antimicrobials used in routine animal farming, combined with the quantity released through animal excretions, can exert selective pressure on local bacterial populations. This pressure, whether through spontaneous or acquired mutations, or horizontal gene transfer, promotes the survival and persistence of these populations, making these environments hotspots for resistance. From these locations, the dissemination of these genes, microorganisms, and/or compounds is facilitated by the movement of water in natural bodies such as rivers and lakes, eventually reaching environments close to the water flow (Bobate *et al.*, 2023; Larsson & Flach, 2022). However, as mentioned earlier, most of the information comes from states or regions that concentrate animal production.

The soil microbiota can serve as an initial contributor to microorganisms and resistance genes related to clinical pathogens, reinforcing the One Health perspective. This is because some resistance mechanisms to compounds found in soil, such as metals, biocides, and

pesticides—especially those present in plasmid-based genetic material, like β -Lactams Resistance-ESBL and Plasmid-Mediated AmpC (pAmpC)—confer cross-resistance to some of the major classes of antibiotics, such as aminoglycosides, anphenicols, β -lactams, sulfonamides, and tetracyclines (Forsberg *et al.*, 2012; Ranganamy *et al.*, 2017). This horizontal gene transfer has been evidenced in Brazilian studies where the presence of microorganisms resistant to quinolones, sulfonamides, aminoglycosides, tetracyclines, and β -lactams in poultry and swine farming exceeds, in most cases, half of the resistant isolates found in studies conducted in the last decade, with a particular emphasis on studies conducted in the southern, southeastern, and northeastern regions (Rabello *et al.*, 2020).

Cattle farms are considered an emerging health issue as a whole, as they serve as significant reservoirs of resistance genes, especially those carried by mobile genetic elements, among microorganisms belonging to Proteobacteria, Bacteroidetes, Actinobacteria, and Firmicutes (Xu *et al.*, 2022). The route of dissemination of genes such as *bla* (conferring resistance to β -lactams), *aac* (conferring resistance to aminoglycosides), *tet* (conferring resistance to tetracyclines), *sul* (conferring resistance to sulfonamides), *erm* (conferring resistance to macrolide-lincosamide-streptogramin), *fca* (conferring resistance to fluoroquinolones, quinolones, florfenicol, chloramphenicol, and anfenicol), *van* (conferring resistance to vancomycin), *mcr* (conferring resistance to colistin), as well as genes conferring resistance to multiple antimicrobials, has been frequently associated with direct or indirect contact between humans and animals, as well as exposure to contaminated products and waste such as feces, water, and animal-derived food products, or inhalation of aerosols (He *et al.*, 2020; Larsson & Flach, 2022).

Aquaculture is a hotspot that has threatened both human and animal health, as several studies have highlighted the presence of antimicrobial resistance genes in intestinal bacteria from shrimp in China and tilapia cultivars in Costa Rica. These genes are linked to antibiotics such as tetracyclines, quinolones, sulfadiazine, and erythromycin (Oviedo-Bolaños *et al.*, 2021, Liu *et al.*, 2019). Studies conducted on shrimp and bivalve farms in the northeastern region of Brazil have demonstrated the presence of resistance genes to tetracyclines, nitrofurantoin, and ampicillin in more than 90% of *Vibrio* spp. isolates, likely mediated by the presence of plasmids (Rebouças *et al.*, 2011; Silva *et al.*, 2018).

Interestingly, bivalves can serve as bioindicator organisms for the presence of antibiotic residues in aquatic environments. This further impacts their potential to act as reservoirs for antimicrobial resistance genes, promoting the dissemination of these genes through water

bodies (Baralla *et al.*, 2021). Resistance genes to colistin and tetracycline have also been identified in mussels and shrimp produced and marketed in the southeastern region of Brazil. These organisms exhibited a phenotypic resistance profile to β -lactams and quinolones, which were associated with *E. coli* isolates (Link *et al.*, 2024).

In order to increase productivity, various chemical substances can be used to pest control in plants or animals. Brazil is the largest importer and consumer of agrochemicals or pesticides, and the increment in the use of these products in recent years has been justified to the increase in the demand for food, as well as to the intensification in the occurrence of plagues (Mattei & Michellon, 2021). In the last Agricultural Census in Brazil, 33.1% of agricultural establishments used pesticides, with the regions South and Northeast presenting the highest number of establishments using pesticides (IBGE, 2017). There are several studies indicating the problems of the indiscriminate use of pesticides, and their implications in the evolution of AMR (Fernandes *et al.*, 2020; Pignati *et al.*, 2017; Moraes, 2019; CETESB 2018a; CETESB, 2018b; Rego *et al.*, 2022).

Nowadays, it is observed that pesticide residues are spreading in the environment, contaminating different ecosystems and compromising food and water resources. The unbridled use of pesticides in the last century aroused the concern of governments and the world population, which led to the prohibition of the commercialization and production of some of them in several countries between the 70s and 80s (Carvalho, 2017). However, most pesticides used in Brazil are toxic, bioaccumulating and prone to long range transport (Fernandes *et al.*, 2020).

Pesticides are associated with antimicrobial resistance in the soil, since, when they contaminate ecosystems, they act on the selective pressure of resistant strains, altering the structure of bacterial communities and environmental resistomes (Malagón-Rojas *et al.*, 2020). It is emphasized that, in the same environment, there may be a mixture of pesticides, as well as the mixture of pesticides with other types of emerging contaminants, leading to the induction of cross-resistance (Curutiu *et al.*, 2017; Malagón-Rojas *et al.*, 2020). Furthermore, the addition of the herbicide to a soil already containing antibiotic residues, even at relatively low concentrations, may already be enough for the selection of resistant strains (Curutiu *et al.*, 2017).

There is a clear relationship between multidrug resistance in bacteria and the presence of pesticides in the soil. For example, bacteria of the genus *Bacillus* degrading monocrotophos, an organophosphate insecticide already banned from United States and European Union, were isolated from a soil used for agricultural activity. Microorganisms resistant to

commonly used antimicrobial like ampicillin, streptomycin, cefotaxime, tetracyclines and chloramphenicol has been described (Rangasamy *et al.*, 2017).

Changes in the response to antimicrobials have already been observed in bacterial strains, exposed simultaneously in vitro to antimicrobials and pesticides. An increase in the minimum inhibitory concentration of the antibiotic aztreonam was observed against strains of *Pseudomonas aeruginosa* isolated from the soil, when exposed to two herbicides widely used, atrazine and diuron (Braz *et al.*, 2019; Kurenbach *et al.*, 2015).

In a study conducted in Brazil, Kurenbach *et al.* (2015) observed changes in tolerance to antimicrobials of different classes, through changes in their minimum inhibitory concentration associated with increased expression of efflux pumps, after exposing strains of *Escherichia coli* and *Salmonella enterica* (Typhimurium) to sublethal concentrations of three herbicides in its commercial formulations: 2,4-D, glyphosate (Roundup®) and dicamba (Kamba®). In *S. enterica*, increased tolerance to ampicillin, chloramphenicol, ciprofloxacin and tetracycline was observed after exposure to dicamba and 2,4-D, and increased tolerance to ciprofloxacin and kanamycin after exposure to glyphosate. Similar responses were found for *E. coli*, but without increased tolerance to ampicillin after exposure to dicamba and 2,4-D.

An approach without the use of pesticides is used by organic agriculture, seeking to maintain the health of soil and ecosystems. This practice has been implemented globally, including in Brazil, although it corresponds to a reduced number of agricultural establishments compared to the conventional practice (Mattei & Michelon, 2021). However, as in conventional agriculture, organic agriculture can also make the soil microbiome susceptible to the development of antimicrobial resistance, mainly through organic fertilization.

The common agricultural practice of fertilizing soils with organic waste, such as animal manure, leads to the dispersion and propagation of ARGs in the environment (Zhang *et al.*, 2017; Sanz *et al.*, 2022). In an experimental study of microcosms with three treatments using agricultural soil, animal manure (poultry, cattle and pigs) and the antibiotic tylosin, interesting results were encountered regarding ARGs. Results indicated that the diversity and abundance of ARGs increased after the application of manure and tylosin-enriched manure, mainly poultry and swine. The genes found can confer resistance to eight classes of antibiotics, of which macrolides, lincosamides, and group B streptogramin, antibiotics called MLSb, and aminoglycosides were the most frequently detected (Zhang *et al.*, 2017).

CONCLUSIONS AND PERSPECTIVES

The aforementioned activities are believed to be associated with the considerable rise of resistant pathogens and could also be associated with the indiscriminate use of antimicrobials. This resistance represents a threat to the development of our society. Our environment is a fundamental part of the evolution and transmission of resistance, and the future of the development of activities that could be called environment friendly need to address some or all of the following steps: The development of novel technologies of antimicrobial removal from key environments, as well as the search for alternatives with less environmental impact and with lesser selective pressure, in order to generate fewer resistant strains.

Also, the support from governance in studies focusing on the mechanism of degradation of compounds used as pesticides so that they could not be persistent in environments are also welcome, along with the investment on other forms of ecological and non-pervasive activities such as environmental tourism and other sources of food that uses less chemicals, with the Agroecology and One Health concepts holding hands.

The scarcity of studies that can correctly evaluate the emission of non-antimicrobial compounds to the environment and their direct or indirect contribution to the emergence of cross resistance between different microorganisms requires that this topic enters the research labs as a major concern for future proposals and long-term projects. The answer to these questions requires scientific research, monitoring, evaluation of impact, and they are a good reminder that the resistance to antimicrobials is an emergency that simply didn't ring the bell yet.

AUTHOR CONTRIBUTIONS

MAR: Writing and English Proofreading; **AJR:** Writing and Correction; **ASAM:** Manuscript elaboration; **APFCF:** Manuscript elaboration; **DVB:** Manuscript elaboration; **LSF:** Manuscript elaboration; **MQS:** Manuscript elaboration; **RMB:** Manuscript elaboration; **FMRSJ:** Critical Correction; **PEAS:** Critical Correction; **DFR:** Original Idea, Writing and Correction.

ACKNOWLEDGEMENTS

Authors are grateful to the National Research Council (CNPq), to the Coordination of Superior Level Staff Improvement (CAPES), to the Rio Grande do Sul Research Support Foundation (FAPERGS) and the National Institute of Health (NIH) for the support.

Conflict of Interest: Not applicable

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