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JOÃO VITOR DOS ANJOS REIS

RESISTÊNCIA ANTIMICROBIANA NA COSTA BRASILEIRA

ARRAIAL DO CABO / RJ
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RESISTÊNCIA ANTIMICROBIANA NA COSTA BRASILEIRA

Dissertação apresentada ao Instituto de Estudos do Mar Almirante Paulo Moreira e à Universidade Federal Fluminense, como requisito parcial para a obtenção do grau de Mestre em Biotecnologia Marinha.

Orientador: Dr. Lohengrin Dias de Almeida Fernandes
Co Orientador: Dr. Sávio Henrique Calazans

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Essa conquista é nossa!

RESUMO

A resistência antimicrobiana (RAM) ocorre quando microrganismos desenvolvem mecanismos para resistir a antimicrobianos, tornando os tratamentos ineficazes e representando uma ameaça global à saúde pública. O uso não regulamentado de antibióticos na agroindústria contribui para o aumento da RAM, especialmente em ambientes marinhos, onde a água de lastro de navios facilita a disseminação de microrganismos resistentes. Portos, como os no Brasil, são pontos críticos para essa propagação devido à presença de grandes bacias fluviais e ao despejo de resíduos. Foram analisadas 92 publicações sobre RAM nas áreas costeiras e marinhas do Brasil no período de 2010 a 2022. Apesar de um aumento gradual na produção científica, o tema ainda é subexplorado no país.Esta revisão analisa dados sobre genes e fenótipos de resistência antimicrobiana (RAM) detectados ao longo da costa brasileira entre 2010 e 2022, destacando lacunas críticas e oferecendo direções para pesquisas futuras. Dos 55 antibióticos utilizados pelos trabalhos copilados, apenas 13 foram classificados como criticamente importante sendo a única ou uma das limitadas terapias disponíveis para tratar infecções bacterianas graves em pessoas ou em animais pela Organização Mundial da Saúde (OMS) e pela Organização Mundial de Saúde Animal (OIE), respectivamente. A classe dos β-lactâmicos recebeu atenção considerável nas pesquisas; no entanto, o gene mais frequentemente detectado foi o *sul1*, pertencente à classe das sulfonamidas. Observou-se uma distribuição geográfica heterogênea dos estudos, com a maioria concentrada na região Sudeste, seguida pelas regiões Nordeste, Sul e Norte. Os estudos identificaram genes de resistência e evidenciaram a necessidade de investigações sobre suas interações com fenótipos. A resistência também está associada a antibióticos em sedimentos e água de lastro. Embora testes fenotípicos predominem, eles frequentemente negligenciam antibióticos críticos listados pela OMS, e estudos em portos e áreas urbanizadas são escassos. O aumento da RAM em ambientes marinhos brasileiros requer vigilância de espécies hospedeiras, especialmente migratórias, e pesquisas multidisciplinares para monitorar a presença de RAM em água, sedimentos e organismos. A implementação de estudos mais abrangentes e alinhados às prioridades globais é essencial para enfrentar os desafios da RAM.

Palavras-chave: eDNA, resistoma, transferência horizontal de genes, drogas, biofilme, poluição

ABSTRACT

Antimicrobial resistance (AMR) occurs when microorganisms develop mechanisms to resist medications, rendering treatments ineffective and posing a global public health threat. The unregulated use of antibiotics in agro-industry contributes to the increase in AMR, especially in marine environments, where ship ballast water facilitates the spread of resistant microorganisms. Ports, such as those in Brazil, are critical points for this dissemination due to the presence of large river basins and waste discharge.A total of 92 publications on AMR in Brazil's coastal and marine areas between 2010 and 2022 were analyzed. Despite a gradual increase in scientific output, the topic remains underexplored in the country. This review examines data on antimicrobial resistance (AMR) genes and phenotypes detected along the Brazilian coast from 2010 to 2022, highlighting critical gaps and offering directions for future research. Of the 55 antibiotics tested, only 13 were listed as priorities by the World Health Organization (WHO) and the World Organisation for Animal Health (OIE). The β-lactam class received considerable research attention; however, the most frequently detected gene was *sul1*, belonging to the sulfonamide class. There was a heterogeneous geographical distribution of studies, with most concentrated in the Southeast region, followed by the Northeast, South, and North regions. The studies identified significant resistance genes and underscored the need for investigations into their interactions with phenotypes. Resistance was also associated with chemical compounds in sediments and ballast water. Although phenotypic tests predominate, they often overlook critical antibiotics listed by WHO, and studies in ports and urbanized areas are scarce. The increase in AMR in Brazilian marine environments requires monitoring of host species, particularly migratory ones, and multidisciplinary research to assess the presence of AMR in water, sediments, and organisms. The implementation of more comprehensive studies aligned with global priorities is essential to address the challenges of AMR.

Keywords: eDNA, resistome, horizontal gene transfer, drugs, biofilm, pollution

SUMÁRIO

Sumário

Lista de abreviaturas e Siglas

AMR	Antimicrobial Resistance (Resistência Antimicrobiana)
BRAs	Bactérias Resistentes a Antibióticos
eDNA	Environmental DNA (DNA ambiental)
EPM	Efflux Pumps (Bombas de efluxo)
GRAs	Genes Resistentes a Antibióticos
HGT	Horizontal Gene Transfer (Transferência Horizontal de Genes)
MDR	Multidrug Resistance Genes (Genes de Resistência a Múltiplos Fármacos)
OIE	World Organization for Animal Health (Organização Mundial da Saúde Animal)
RAM	Resistência Antimicrobiana
WHO	World Health Organization (Organização Mundial da Saúde)

INTRODUÇÃO GERAL

O ambiente marinho é um potencial reservatório de genes de resistência a antibióticos (ARGs) devido aos efeitos antropogênicos decorrentes do lançamento de águas residuais, esgotos domésticos e hospitalares e efluentes agroindustriais em corpos d'água que eventualmente chegam até o mar (Tuvo *et al*., 2023; Mortensen *et al*., 2024; Schages *et al*., 2020). Este problema é especialmente preocupante em países como o Brasil, onde a agricultura é extensiva e o uso de antibióticos é frequente para uma grande parte da população (Shen *et al.*, 2023). Esses ambientes são ideais para a aquisição e disseminação de GRAs, que aumentam a exposição de bactérias resistentes a antibióticos (BRAs) em ambientes aquáticos, o que representa um risco adicional à saúde pública, especialmente no consumo de produtos marinhos.

O escoamento costeiro de BRAs e GRAs provenientes de fontes terrestres é apontado como um dos principais mecanismos que favorecem a ocorrência de resistência a antibióticos em ambientes marinhos (Hatosy & Martiny, 2015). Relatórios recentes destacam a contaminação global de ambientes aquáticos por antibióticos, o que sugere o desenvolvimento de microrganismos resistentes, inclusive em oceanos abertos (Shin et al., 2022; Zhang *et al*., 2024; Ya *et al*., 2023).

). Segundo Corno e colaboradores (2019) o uso de antibióticos aumenta a pressão seletiva em diferentes ecossistemas. Microrganismos resistentes estão em rios e lagos, áreas de maior acúmulo de GRAs. Além disso, estudos identificaram microrganismos resistentes em ambientes marinhos, em regiões próximas a descargas de rios. O artigo de revisão destaca que vários genes resistentes a carbapenêmicos (CRGs) foram detectados em diferentes ambientes marinhos, com a maioria dos genes incorporados em elementos genéticos móveis, ou seja, transposons ou plasmídeos, que podem contribuir para uma transferência genética eficiente (Dewi *et al*., 2021).

Evidências crescentes mostram que eventos climáticos extremos, como, aumento da temperatura da superfície do mar e descarga antropogênica, exacerbam a disseminação de doenças relacionadas a microrganismos nas Américas e na Ásia. Esses fatores também facilitam o deslocamento de organismos marinhos portadores de genes de resistência provenientes de áreas distantes (Martinez-Urtaza *et al*., 2016). Embora esses genes não sejam transportados facilmente por vias naturais, as atividades humanas nos últimos 100 anos, como turismo e transporte global de cargas, têm facilitado a mobilização de células contendo GRAs (Zhu *et al*., 2017). Esses fenômenos, aliados ao transporte de microrganismos por atividades marítimas, agropecuárias e saúde humana e animal, criam hotspots de resistência. Assim, bactérias desenvolvem resistência e disseminam genes entre outros microrganismos nos locais, mesmo na ausência de agentes seletivos (Marti, Variatza & Balcazar, 2014), intensificando a disseminação de doenças transmitidas pela água em uma rede de transporte internacional dinâmica e interconectada.

A rede internacional de disseminação de doenças inclui, por exemplo, áreas portuárias e tanques de lastro de navios. A água de lastro dos navios pode transportar microrganismos patogênicos e introduzi-los em novos ambientes. A água de lastro é usada pelos navios para manter a estabilidade e o equilíbrio, mas pode transportar inadvertidamente espécies invasoras, incluindo bactérias e microrganismos nocivos, de um local para outro. Esses patógenos podem então proliferar no ambiente do contêiner e representar um sério risco à saúde humana (Cabral, 2010; Lakshmi *et al*., 2021). Os microplásticos na água de lastro também podem servir como um vetor para a transferência de patógenos multirresistentes (MDR) entre continentes. de patógenos para o ambiente local (Yang *et al*., 2022). Por tanto áreas como portos, estuários e tanques de lastro de navios são propícios à formação de biofilmes microbianos, que permanecem nos sedimentos e águas residuais mesmo após o deslastre (Drake, 2007). Outrossim, o transporte de microrganismos pela água de lastro pode causar bioinvasões, que levam a introdução de genes de resistência provenientes de diferentes locais (Baier, 2014). Estudos recentes destacam os impactos econômicos, ambientais e de saúde pública das bioinvasões, especialmente em regiões portuárias, lacustres e marinhas (David *et al*., 2007; Emami *et al*., 2012; Câmara & Fernandes, 2019).

OBJETIVO GERAL

A pesquisa "**Resistência Antimicrobiana na Costa Brasileira**" visa a evidenciar alguns dos *gaps* sobre resistência antimicrobiana na costa brasileira nos últimos doze anos, através do levantamento de artigos que detectaram genes de resistência ao longo deste período.

OBJETIVOS ESPECÍFICOS

- Gerar um mapa com as fontes de isolamento de microrganismos resistentes associando bacias hidrográficas e suas fozes, densidade demográfica e principais portos

- Evidenciar quais as principais fontes de isolamento, microrganismos isolados, antibióticos mais utilizados, genes mais procurados e detectados.

- Avaliar se os artigos seguem as recomendações de quais antibióticos são mais relevantes segundo a Organização Mundial de Saúde e Organização Mundial de Saúde Animal.

ABSTRACT

Coastal runoff of antimicrobial resistance (AMR) is a major driver of the emergence and dissemination of antibiotic resistance in marine environments, impacting human, environmental health, and economic sectors. This review analyzes data on AMR genes and phenotypes detected along the Brazilian coast from 2010 to 2022, highlighting critical *gaps* and offering directions for future research. Among the 55 antibiotics considered for this review, only 13 were listed as priorities by the World Health Organization (WHO) and the World Organization for Animal Health (OIE). The most frequently detected gene was *sul*1, from the sulfonamide class. There was a heterogeneous geographical distribution of studies, with the majority concentrated in the Southeast, followed by the Northeast, South, and North regions.

Keywords: eDNA, resistome, horizontal gene transfer, drugs, biofilm, pollution

1. INTRODUCTION

Antimicrobial Resistance (AMR) occurs when microorganisms develop mechanisms to resist drugs and chemicals typically used for treatment infections (Mackenzie & Jeggo, 2019; Berglund, 2015; Reichert *et al*., 2019; Salam *et al*., 2023). This resistance renders treatments ineffective, increasing the risk of new infections (Mackenzie & Jeggo, 2019). Consequently, AMR has become a significant global public health threat (World Health Organization, 2015; Salam *et al*., 2023; Walsh *et al*., 2023), as emphasized by the United Nations' 'One Health' paradigm. AMR is a worldwide issue that impacts all regions and populations (Salam *et al*., 2023) and involves multiple sectors (Mackenzie & Jeggo, 2019), necessitating comprehensive data collection from human and animal health as well as environmental domains.

The use of antibiotics and antimicrobial chemicals is crucial in agro-industrial production to protect cultures against diseases and to increase farm yields (Landers *et al*., 2012; Da Costa *et al*., 2013). However, the fate of microbial populations under periodic antimicrobial exposure has implications for marine sediments, where antimicrobial compounds may be periodically introduced through human activities. (Marrec e Bitbol 2020) This could contribute to the development of resistant strains in these environments, significantly impacting ecosystem dynamics, particularly through discharge into wastewater, domestic and hospital sewage, and agricultural runoff (Li *et al*., 2020).Coastal runoff from land-based sources is a recognized pathway for the occurrence and spread of antibiotic resistance in marine environments (Lu *et al*., 2015; O'Flaherty & Cummins, 2017; Jang *et al*., 2018). These discharge processes ultimately lead to rivers and estuaries, where ports are commonly established.

Ports and anchorages are critical areas where ships must load or unload large volumes of ballast water (up to 60,000 tons per ship) for stability and safe navigation. Ballast water serves as a major vehicle for spreading microorganisms and can disperse resistance genes, making coastal regions vulnerable to unwanted species (Bradie *et al*., 2023; Drake *et al*., 2007; Zheng *et al*., 2021). Currently, global trade relies heavily on cargo ships, which transport an estimated 3.5 billion tons of ballast water annually (Yilmaz & Bilgin, 2022). In addition to imported water, port areas also receive significant continental runoff, especially from rivers that flow through large farms and populated regions (Landers *et al*., 2012; Da Costa *et al*., 2013).

In Brazil, the three largest river basins (Amazon, Tocantins-Araguaia and São Francisco) flow into tropical regions with warm waters, creating conditions conducive to the possible accumulation of resistant microorganisms. Marine and coastal areas are known to serve as reservoirs for resistance genes that provide organisms with antimicrobial resistance profile (AMR) (Dewi et al., 2021; Lv *et al*., 2020; Lv et al., 2021).

The accumulation of AMR in coastal regions and ships (Yang et al., 2019; Yang et al., 2021) is often evidenced by the presence of antibiotic resistance genes (ARG), which facilitate the spread of resistance factors and influence the ecology and evolution of microbial communities (Corona & Martinez, 2013; Sivalingam, Poté, & Prabakar, 2020; Sekyere & Faife, 2021). A crucial process in the spread of AMR is Horizontal Gene Transfer (HGT), where mobile genetic elements (transposons) are transfered between microorganisms across species (Corona & Martinez, 2013; Marin et al., 2014; Sivalingam, Poté, & Prabakar, 2020).

Horizontal gene transfer (HGT) is a crucial process in the spread of antimicrobial resistance (AMR). Mobile genetic elements (MGEs), such as transposons, play a key role in facilitating the dissemination of genetic resistance determinants across diverse environments and clinical settings (Hall *et al*., 2017). MGE, including insertion sequences, transposons, integrons, and plasmids can transfer antibiotic resistance genes between microorganisms of different species and genera through three main mechanisms: conjugation, transformation, and transduction (Hall *et al*., 2017). The spread of drug resistance genes among microorganisms through plasmid-mediated conjugation transfer is considered the most common and effective way for the dissemination of multidrug resistance (Tao *et al*., 2022). While in vitro experimental studies have focused on the processes driving the spread of antibiotic resistance, in vivo models can better mimic the situation that occurs in patients and help study the HGT of antibiotic resistance genes in more detail (Tao *et al*., 2022). HGT is not the only way for the spread of AMR, but it is considered a major contributor, as it facilitates the rapid dissemination of novel ecological traits within and between bacterial species. (Hall *et al*., 2017; Widen *et al*., 2023).

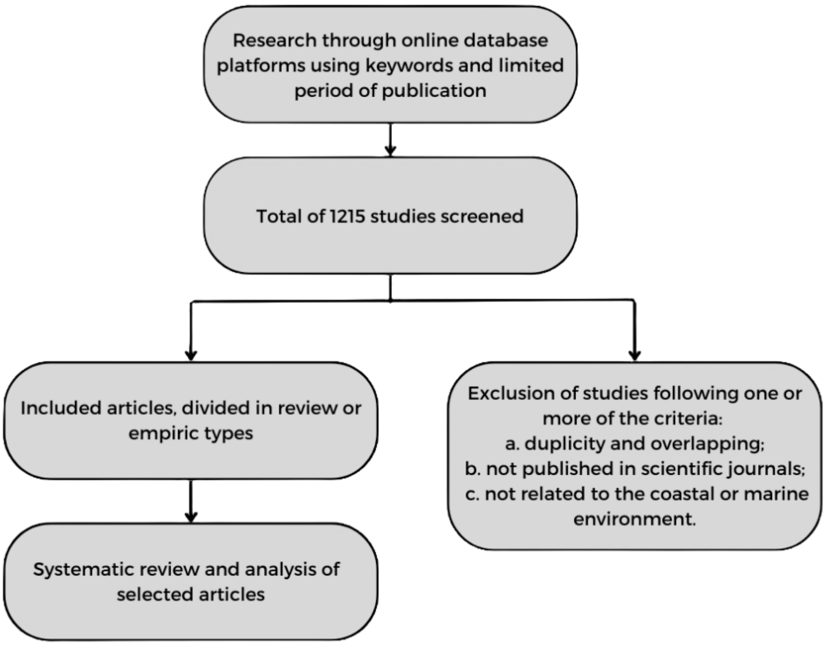
Environmental pollution amplifies this process, affecting the genetic makeup and phenotypes of resident microbiota (Mackenzie & Jeggo, 2019; World Health Organization et al., 2015; Gajdács *et al*., 2021; Liguori *et al*., 2022).

This review aims to: (1) examine recent literature (2010-2022) on the status of AMR in Brazil's coastal and marine areas; (2) highlight sources of isolation, geographic distribution, identified resistant genes, and predominant antibiotics used in antimicrobial tests; and (3) identify research gaps in regions with a higher risk of AMR spread, based on demographic factors and proximity of river basins to major Brazilian ports.

2. MATERIALS AND METHODS

The literature search was conducted using Web of Science, Scopus, Google Scholar, and Litmaps with the keywords “Brazil” or “Brazilian,” “Antimicrobial Resistance Genes,” and variables “Marine,” “Coast,” and “Estuary” in both English and Portuguese (**Fig**.1). Monographs, dissertations, theses, conference abstracts, and technical reports were excluded as non-peer-reviewed literature. The search focused on publications from the past 12 years (2010 to 2022) reporting resistance genes or phenotypes along the Brazilian coast. Studies analyzing samples from environmental sources (sediment, water, organisms) and adjacent areas like rivers and brackish lakes were included. Priority was given to the following information: year of publication, year of sampling, location, source of isolation of microorganisms or environmental DNA, tested antibiotics, antibiotic resistance, and resistance genes. The methodology for antimicrobial susceptibility testing used in the compiled studies was not taken into account, only the data from the results were extracted.

Figure 1 – Diagram with steps of the scientific research approach.



The diagram shows the workflow and the screening method used for selecting scientific articles for data extraction

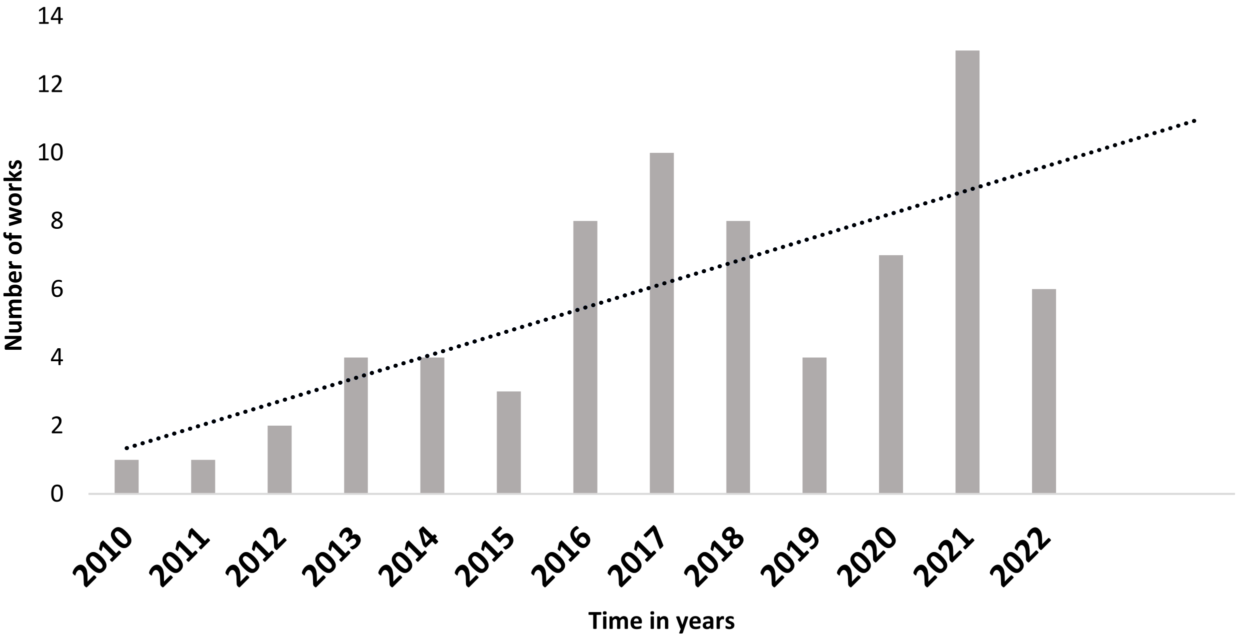
3. RESULTS AND DISCUSSION

A total of 92 from 177 publications were considered in this study, 21 of which are reviews and the remaining 71 are original research articles used for data extraction. Only four articles did not provide the year of sample collection. In these cases, the year of publication was used as a substitute. One study did not specify the exact sampling location, although it indicated the Brazilian State where the research was conducted. A study reporting samples collected in two different States of Brazil was intentionally duplicated in the table of publications and the respective resistance genes were attributed to each State where they were detected.

3.1 Scientific production over time

The number of publications showed a gradual increase with some fluctuations over time (**Fig**. 2). The gradual increase in scientific production observed over the years suggests that studies focusing on the environmental spread of AMR remain under-explored in Brazil. Globally, in contrast, there is a significant increase in publications from the early 2000s to 2018, indicating a focus on the potential anthropogenic effects of AMR associated with animals and food (Torres *et al*. 2021). Overall, there was an increase in publications regarding AMR in the 2020s decade in South America, likely due to the growing global awareness of the risks associated with Antimicrobial Resistance Genes (ARGs) (Torres *et al*., 2021; Zheng *et al*., 2021).

Figure 2 – Annual scientific production (number of publications per year) in the Brazilian Coast.



The graph shows the increasing trend in scientific production on studies related to antimicrobial resistance over a 12-year period along the Brazilian coast.

The year of 2021 had the greatest effort on investigating AMR in the Brazilian Coast, with a total of 13 articles published (**Fig**. 2) coincident with the launch of the United Nations Decade of Ocean Science for Sustainable Development (Ryabinin *et al*., 2019). Additionally, some significant global events occurred during the period analyzed, such as the announcement of the United Nations 2030 Agenda and the COVID-19 pandemic in 2020-2021. In this context, AMR was identified as a factor that could hinder progress towards achieving the Sustainable Development Goals (Gajdács *et al*., 2021). Furthermore, during the pandemic, the prevalence of AMR increased among patients with bacterial co-infections, exacerbated by the excessive use of antibiotics (Ghosh; Bornman; Zafer, 2021; Kariyawasam *et al*., 2022).

3.2 Perspective of reviews found

Of the total studies analyzed, 21 were classified as review articles. Among these, 12 articles (57%) providing a global overview and identifying Brazil as a potential convergence zone for antimicrobial resistance profiles. Many highlighted a research gap in underdeveloped countries in South America, Africa, and Asia (Baker-Austin, 2015; Domínguez; Chacón; Wallace, 2021). Some reviews emphasized the need for standardization of techniques and monitoring, recommending metagenomics for better understanding antimicrobial resistance in water bodies, and phenotypic techniques for clinically relevant microorganisms (Elmahdi; Dasilva; Parveen, 2016; O'flaherty; Cummins, 2017; Sekyere; Faife, 2021; Liguori *et al*., 2022). Several articles noted Horizontal Gene Transfer (HGT) (Marin *et al*., 2014; Berglund, 2015), highlighting hotspots of resistance profiles and the widespread presence of resistance genes in aquatic environments.

Five studies focused on microorganisms, indicating the genus Vibrio, which is cosmopolitan in marine ecosystems, as significant for antimicrobial resistance (Elmahdi; Dasilva; Parveen, 2016). Vibrio species can accumulate and spread resistance genes through conjugative elements such as Salmonella genomic island 1 (SGI1) and its related elements (Schultz *et al*., 2017). Genera such as Shewanella, Pseudomonas, and Klebsiella can also harbor these integrative mobilizable elements, contributing to the dissemination of antibiotic resistance genes (Schultz *et al*., 2017). The spread of these resistance genes across bacterial genera is a significant public health concern, as it can lead to the emergence of multidrug-resistant pathogens (Schultz *et al*., 2017).

This issue is particularly concerning for ESKAPE pathogens (Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter species) (Santaniello *et al*., 2020; Masoud et al., 2022). The acronym ESKAPE was coined to highlight these microorganisms' ability to evade the action of antibiotics, develop antimicrobial resistance, and hinder eradication through conventional therapies (Santaniello *et a*l., 2020). These pathogens are responsible for many hospital-acquired infections and pose a serious threat to human health (Marie *et al*., 2024).

Furthermore, the co-occurrence of resistance genes and virulence factors in these pathogens exacerbates the problem, emphasizing the need for a One Health approach to combat antibiotic resistance effectively.

In Latin America, an article examined antimicrobial resistance, with a survey of contaminants in agricultural wastewater, mainly from pig farms in Brazil, where resistant pathogens were found in feces, soil and water, in farmed fish, such as contaminating tilapia, where they found bacteria resistant to the same five antibiotics most tested in the Brazilian coastal region: tetracycline (TC), amoxicillin (AMOX), norfloxacin (NOR), ampicillin (AMP) and imipenem (IMP) (Reichert *et al*., 2019).Research focused on treated or untreated wastewater and potable or irrigation water, with coastal zones included less frequently (Domínguez; Chacón; Wallace, 2021). Most microbial isolation techniques were used in surface waters. Brazil and Mexico significantly contribute to antimicrobial resistance studies in Latin America, emphasizing hospital environments and freshwater bodies (Domínguez; Chacón; Wallace, 2021). This reflects the role of marine and aquatic environments as reservoirs of resistance profiles (Vats; Kaur; Rishi, 2022) and sites of evolutionary convergence due to residue accumulation and genetic diversity (Coutinho *et al*., 2013).

Only four review articles (19%) reported results specific to Brazil. One study highlighted the most investigated antibiotics: chloramphenicol (81.0%), gentamicin (76.2%), sulfa/trimethoprim (71.4%), ampicillin (61.9%), and tetracycline (71.4%). The highest resistance prevalence was observed for chloramphenicol (58.8%), sulfa/trimethoprim (78.5%), and ampicillin (84.6%). However, these data are still from a general overview including articles from the medical field and diagnosis of infections, with a shortage of studies in open environments.

3.3. Environmental sources of resistant microorganisms

In the context of this review, the majority of studies made in Brazil isolated microorganisms from migratory animals such as penguins, turtles, and seabirds, which helps to understand the secondary dissemination of resistance profiles. Among the manuscripts analysed, 47% isolated microorganisms from water, 28% of them in comparative studies with other elements such as sediment, penguins, and cultured mollusks. Only 6 studies (8%) collected and analyzed AMR in sediments. Nevertheless, more research into this source of RAM is needed, since in sediments most of the exchange of genetic material occurs by horizontal transfer due to the accumulation of eDNA and biofilms (Sivalingam; Poté; Prabakar, 2020). The exchange of genetic material occurs by horizontal transfer due to the accumulation of eDNA and biofilms. Biofilms provide an appropriate environment for increased genetic exchange, as they facilitate close contact between bacterial cells and the presence of eDNA, which is an essential component of the extracellular matrix (Ibáñez de Aldecoa *et al*., 2017). The release of environmental DNA (eDNA) is often coordinated by the microbial population in response to quorum sensing signals, and is linked to the development of natural competence, which enables the uptake of environmental DNA (Ibáñez de Aldecoa *et al*., 2017). Additionally, the proximity of donor and recipient strains within biofilms enhances the exchange of genetic material, including antibiotic resistance, between different bacterial species (Conwell *et al*., 2022). Mechanisms other than autolysis, such as the production of extracellular vesicles, have also been shown to contribute to eDNA release and subsequent horizontal gene transfer in biofilms (Domenech & García, 2018).

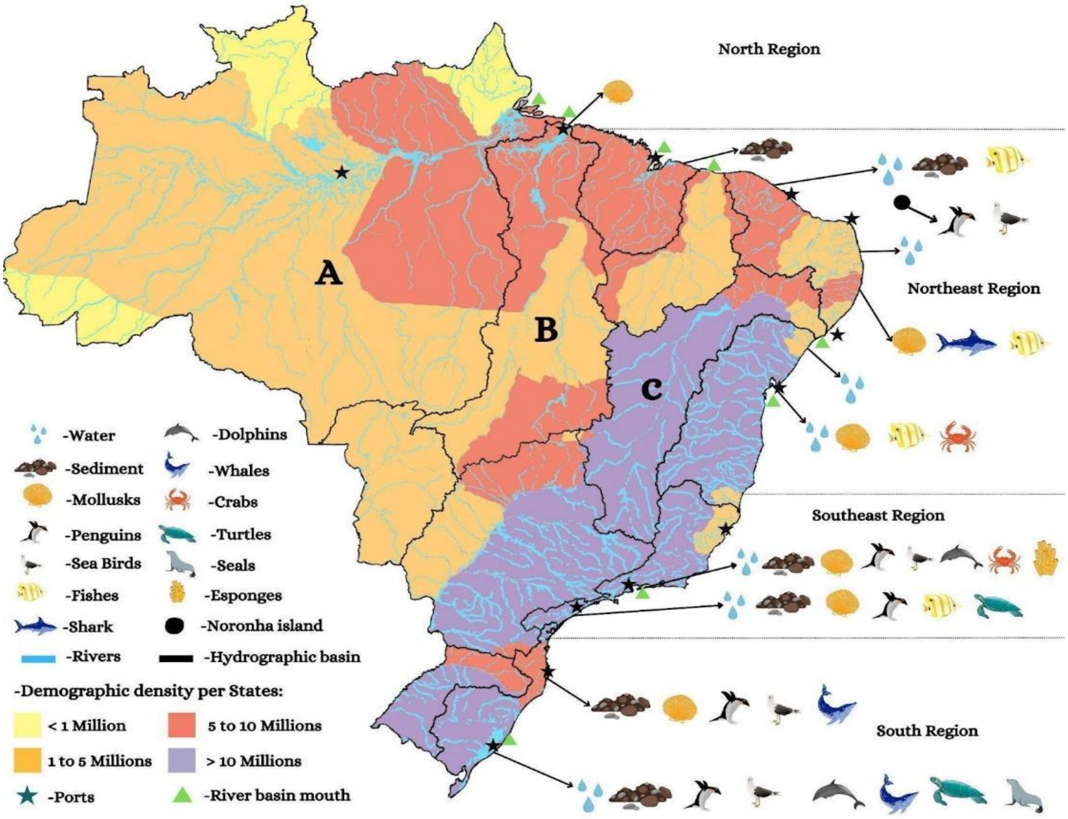
Events of resistance by heavy metals and other compounds can also occur, due to their accumulation at the bottom of coastal marine environments and ballast water sediments (Yang *et al*., 2019).

Only 13 studies on non-migratory organisms focused on filter-feeding mollusks, with 2 studies each on crabs and sponges. Filter-feeding organisms are effective for monitoring resistance profiles in aquatic environments due to their prolonged exposure in areas impacted by urban and agro-industrial wastewater (Karmanova; Zimin, 2020). Sponges are known for their microbial diversity and antimicrobial-producing microorganisms, but they also can harbor resistant bacteria (Laport *et al*., 2016; Leite *et al*., 2019).

Antimicrobial resistance (AMR) is transported to coastal regions through waterways, primarily due to wastewater discharges from hospitals, agriculture, and sewage treatment plants (Singh *et al*., 2022; Sala-Comorera *et al*., 2021). Rivers that flow through urban and agricultural areas become vulnerable, impacting estuarine regions. The estuaries in Brazil's North and Northeast receive water from various rivers, including those near highly urbanized and agricultural zones. However, significant gaps exist in data on AMR in major river basins, such as Amazonas, Tocantins-Araguaia, and São Francisco, particularly in estuarine and port areas like Ponta da Madeira and Itaqui Ports

(São Luís do Maranhão), Port of Belém, Port of Manaus, Port of Natal, and Port of Salvador(**Fig**.3).

Figure 3 – Environmental sources of resistant microorganisms in the last 12 years, in at least one organism.



Letters present the most representative hydrographic basins (A -Amazon River basin; B - Tocantins - Araguaia River basin; C - São Francisco River Hydrographic Basin). Arrows indicate RAM records by State. The marking indicates the outflow of the water basins on the Atlantic coast.

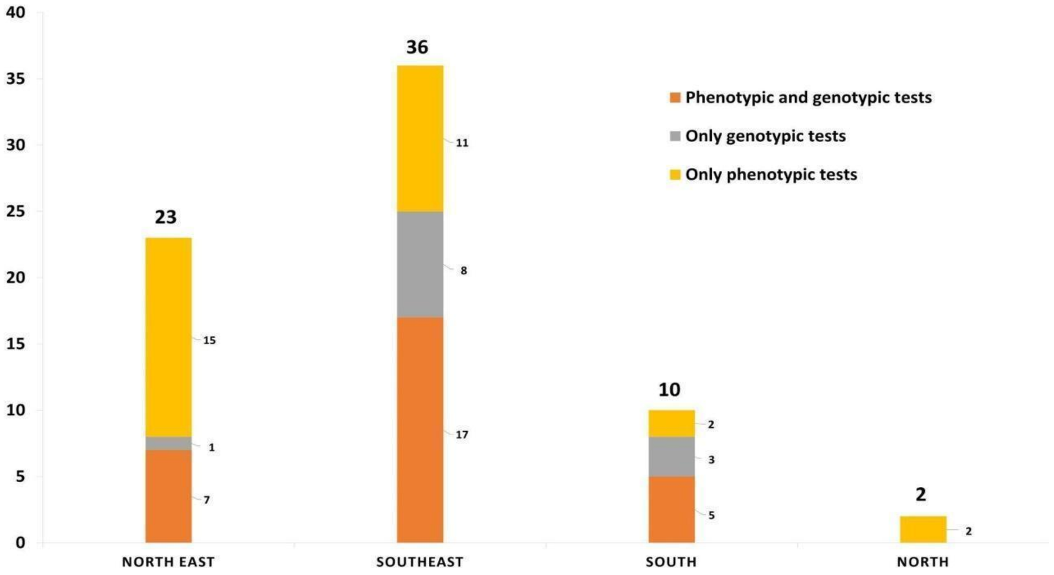
The states of Alagoas, Sergipe, and Pernambuco have urban areas near the coast, alongside port activities and intense tourism, yet lack data on antimicrobial resistance in these coastal environments. This is particularly concerning for Alagoas and Sergipe, located near the São Francisco River estuary, which receives water from various urban centers. Additionally, states like Rio Grande do Norte and Maranhão export economically important products such as salt, soy, and minerals like bauxite and aluminum. This large-scale exportation context is vulnerable to frequent ballast water changes on cargo ships, increasing the risk of bioinvasions by microorganisms resistant to antimicrobial compounds (Lv *et al*., 2020).

The Brazilian coast receives large volumes of ballast water annually (Endresen *et al*., 2004), yet none of the studies focused on AMR biological invasions via ballast water, and few addressed port-related issues. In the Southeast, the State of Espírito Santo, which has around 19 important ports for exporting materials like iron ore, coal, and grains, lacks studies on antimicrobial resistance in coastal or marine environments. Additionally, some states in the North and Northeast, known for their diverse coastal fauna, have few studies on these microorganisms.

In China, country with a strong commercial relationship with Brazil, antibiotic-resistant bacteria were detected in 25 out of 30 samples of ballast water from ships from different places, with a detection rate of 83.3% (Lv *et al*., 2021). In addition, bacteria resistant to penicillin, chloramphenicol, tetracycline, vancomycin, and oxytetracycline were detected in high concentrations in ballast water. The same phenotypes have been found on the Brazilian coast, but little was investigated in terms of spatial distribution (**Fig**. 3) and quantitative aspects. Some of these bacteria are human commensals such as *Vibrio alginolyticus* and *Serratia nematodiphila* and are also resistant to at least three antibiotics. The identification of possible hosts is also very important to understand the gene pools. Coastal aquaculture farms have a predominance of species of the genus *Vibrio* and *Marinomonas,* which are strongly correlated to the tetracycline resistance genes (Jang *et al*., 2018).

Antimicrobial resistance is increasingly being recognized as a problem with ecological dimensions, due to new infections emerging from natural environments (Drane *et al*., 2021; Coutinho *et al*., 2013). The detection map (**Fig**. 3) showed gaps in research on antimicrobial resistance in many States, which is an important issue not only because these locations have ports, but also because of biodiversity, recreational waters, fishing, and mariculture. There is a need for monitoring potential host organisms in countries with extensive coastal areas such as Brazil, including marine animals, because they are the same ones that contract bacterial zoonoses, and especially in migratory species such as turtles, cetaceans, and fish, since they pass through the human food chain (Drane *et al*., 2021; Pereira *et al*., 2020; Kumarage; De Silva; Heo, 2022). Host organisms could also indicate the pathways in which AMR is capable of reaching the marine ecosystem.

Figure 4 – Scientific efforts by region and the profile of experimental tests for detecting resistance profiles.



The graph shows the quality of the investigations, indicating whether they focused solely on genotype, phenotype, or both, separated by region.

Phenotypic tests that rely on the growing of cultures remain the foundation of antimicrobial analysis in Brazil (**Fig**. 4), especially in the marine environment. The antibiogram test is widely used for detection and characterization of antimicrobial resistance profiles. However, this technique has limitations, particularly in environments with a predominance of non-cultivable species, which likely play a significant role in the dissemination and maintenance of resistance profiles in the ecosystem (Liguori *et al.*, 2022). Despite these limitations, growing techniques and antibiogram tests are crucial for analyzing human commensal bacteria and those that transit through the food chain. This justifies the trend observed in this study, which points to the isolation of microorganisms associated with human health, such as *Enterococci*, *E. coli*, vibrios, *Pseudomonas*, and *Aeromonas*, with isolation rates of 22%, 16%, 10%, and 7%, respectively.

The spatial distribution of scientific efforts (Fig. 4) reflects the detection of resistance genes in coastal regions. More studies on antimicrobial resistance were conducted in the northeast region compared with the south region, with greater diversity of genes investigated per study. The same applies to the sources of isolation (Fig. 3). Beta-lactam genes were the most detected due to the diversity of genes explored (Fig. 4), although less frequently studied. Investigations of the *blaTEM, blaCTX−M, blaOXA*, and *blaKPC* genes, which are common in hospital infections, stand out for being among the most detected over the 12-year period. These genes, associated with ESKAPE bacteria, are among the most prevalent in widespread infections in Brazil (Silveira et al., 2021; De Oliveira et al., 2020).3.4. Resistance phenotypes

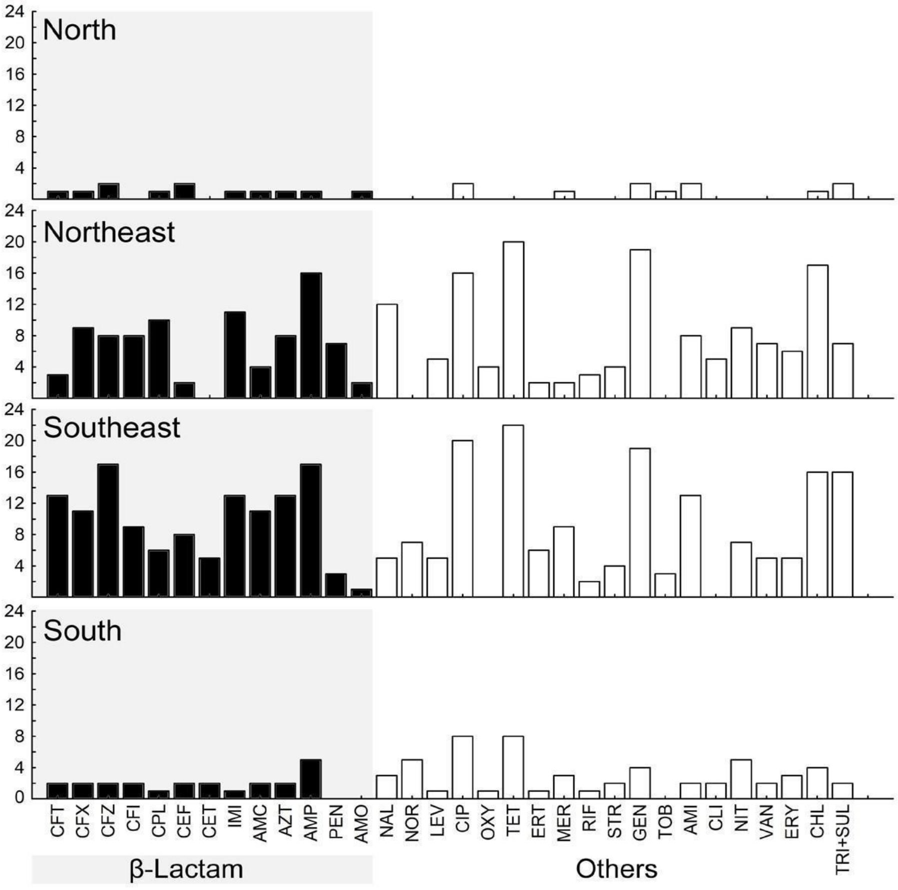
The importance of phenotypic tests lies in understanding the effectiveness of currently used antibiotics and detecting possible resistances to antimicrobial compounds. These resistances may not necessarily be associated with the presence of known resistance genes, but rather with metabolic or morphological adaptations, as already observed in hospital environments (Corona; Martinez, 2013). For a more comprehensive analysis in studies about AMR in Brazil, it is essential that molecular techniques are applied in conjunction with phenotypic techniques, at least within cultivable microorganisms, so that the factors driving resistance can be identified. The discovery of Enterococcus gallinarum, which harbored the vanA and vanC1 gene clusters but did not confer resistance to vancomycin, suggests that similarities in genotypic characteristics may not necessarily correlate with actual antibiotic resistance patterns. This indicates that resistance can arise through mechanisms beyond the presence of known resistance genes, such as structural variations in resistance-conferring elements or other physiological adaptations (Loong et al., 2016). Thus, environmental research should align with the relevance of the most commonly used or clinically important antibiotics, as listed and classified by the World Health Organization (WHO).

The World Health Organization (WHO) classify antibiotics into Critically Important, Highly Important, and Important according to C1 and C2 criteria (World Health Organization *et al*., 2019).

According to the studies analyzed in this review, there is a significant gap in tests related to antimicrobials from the Highly and Critically Important groups. Thirty-one (31) antimicrobials currently in use were rarely (< 3) tested in Brazil. Alarmingly, both the World Health Organization (WHO) and the World Organization for Animal Health (WOAH) (OIE, 2007) classify many of these antibiotics as Highly or Critically Important for treating infections in humans and livestock, including both Highly Important for human health (Chlortetracycline, Quinupristin/Dalfopristin, Trimethoprim, and Sulfadimethoxine) and Critically Important for human health (Azithromycin, Colistin, Daptomycin, Piperacillin, Piperacillin/Tazobactam, Polymyxin, and Polymyxin B). Despite their relevance, they were tested fewer than three times and do not appear in **Fig.** 5 for clarity.

Among the 32 most tested antibiotics in Brazil, 13 belong to the Critically Important group, namely Gentamicin, Rifampicin, Meropenem, Vancomycin, Erythromycin, Aztreonam, Ampicillin, Amoxicillin/clavulanic acid, Ceftriaxone, and Ciprofloxacin, and 3 - Chloramphenicol, Clindamycin, and Trimethoprim/sulfamethoxazole - are considered as Highly Important. Despite the medical relevance of these antibiotics, they have been investigated fewer than 20 times in the Brazilian coastal and marine environment over 12 years. Even in the Southeast region, which has the majority of studies, antimicrobial tests do not consistently follow the lists of the OIE and WHO (**Figs.** 4 e 5).

Figure 5 – Most tested antibiotics in the last 12 years distributed along the Brazilian coast.



Lactam (AMC) = amoxicillin/clavulanic acid**, AMO =** amoxicillin**, AMP** = ampicillin**, AZT =** aztreonam**, CEF =** cefepime**, CET =** ceftiofur**, CFI =** ceftriaxon**, CFT** = cefotaxim**, CFX =** cefoxitin**, CFZ =** ceftazidim**, CPL =** cephalothin**, IMI =** imipenem**, PEN =** penicillin. **Other Classes - AMI =** amikacin**, CHL =** Chloramphenicol**, CIP** = ciprofloxacin**, CLI =** Clindamycin**, ERT** = ertapenem**, ERY** = erythromycin**, GEN** = gentamicin**, LEV** = levofloxacin**, MER** = meropenem**, NAL = nalidixic acid, NIT** = nitrofurantoin**, NOR** = norfloxacin**, OXY** = oxytetracycline**, RIF = rifampicin, STR =** streptomycin**, TET** = tetracycline**, TOB** = tobramycin**, TRI+SUL =** trimethoprim/sulfamethoxazole**, VAN =** vancomycin**.**

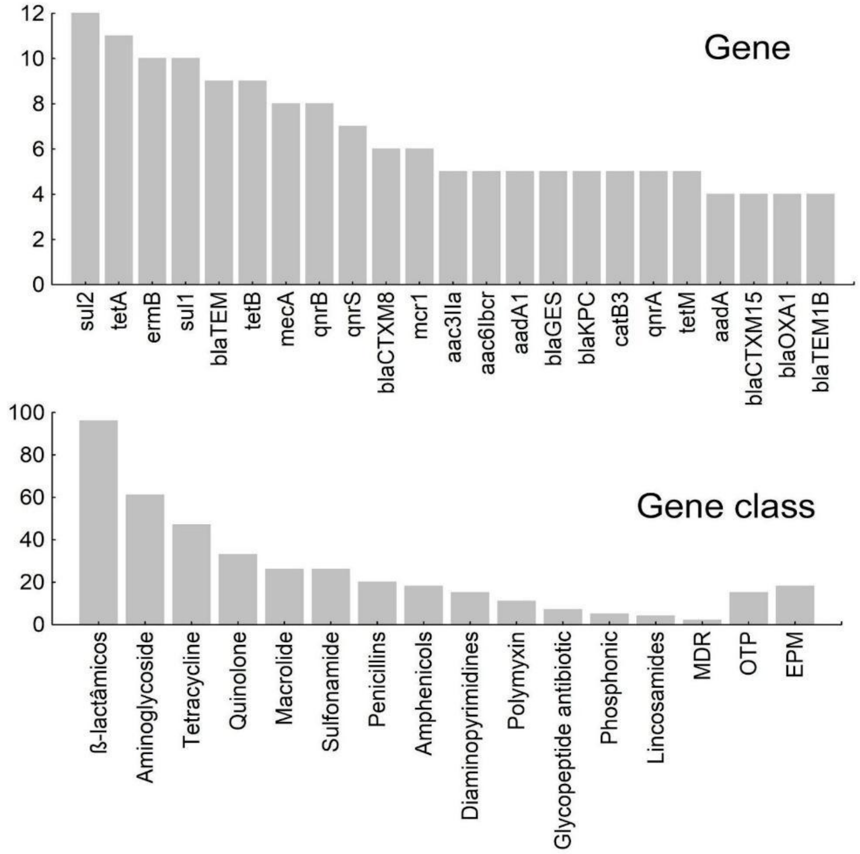
Regarding beta-lactams (Amoxicillin/clavulanic acid), a combination with a beta-lactamase inhibitor administered orally or intravenously shows effectiveness against beta-lactam-resistant bacteria and is classified as Critically Important by WHO. However, this antibiotic was tested only 11 times in the Southeast region and less than four times in other regions during the analyzed period (**Fig.** 5). In addition to the observed gap in phenotypic antimicrobial testing, it is clear that most of the antibiotics commonly tested in marine/coastal environments in Brazil are not included in either the WHO or OIE lists. The regional distribution of these antimicrobial tests follows the pattern of studies along the coast, as shown in **Figs**. 3 and 5.

In general, there is a shortage of quantitative studies, especially those that analyze the relationship between resistance genes and the phenotypes observed in cultivable strains. This gap hinders a broader understanding of what might happen in open and coastal marine environments, and the risks associated with economic activities in these regions.

3.5. Resistance genotypes

Sulfonamide resistance genes *sul1* and *sul2* were widely detected, as shown in Fig. 6. They are known to be abundant in ballast tank sediments of ships and in coastal regions of China and Korea (Lu *et al*., 2015; Suzuki *et al*., 2019; Endresen *et al*., 2004). In Brazil, the common use of sulfonamides in aquaculture may explain the frequent detections registered in this study. The scarcity of data highlights vulnerabilities in port regions, as it is already known that these genes are transported by ships on transoceanic voyages (Lv *et al*., 2020; Lv *et al*., 2021). The genes *sul2* and *sul1* are the most detected genes on the Brazilian coast over 12 years, though in a diffuse manner. There is a significant gap for future studies, especially in ballast water microbiota and Brazilian ports such as São Luís do Maranhão, Belém, Manaus, Natal, and Salvador, and at the mouths of major rivers like the Amazon, Tocantins-Araguaia, and São Francisco (Drake, Doblin, & Dobbs, 2007; Bradie *et al*., 2023; Sala-Comorera *et al*., 2021).

Figure 6 – Most detected genes in Brazilian coast.



Gene classes: Number of detected genes grouped into antibiotic classes, included MDR: Multiple Drug Resistance; OTP: Outer Membrane Protein; EPM: Efflux Pump Mediated.

Tetracycline class genes were also widely detected, with *tetA* and *tetB* among the most frequently detected genes (**Fig**. 6). Although there are 38 different tetracycline (tet) and oxytetracycline (otr) genes (Roberts, 2005), only *tetA* and *tetB* have been studied, highlighting the need of updated knowledge about the diversity of these genes along the Brazilian coast. The tetracycline class is crucial for veterinary applications and human health (WHO and OIE) and is also transported by ships, similar to sulfonamide genes (Lv *et al*., 2020). Other genes such as *tetC*, *tetD*, and *tetQ* were also found along the Brazilian coast but appeared only three times in this study . Investigating the genetic diversity of

RAM genes is important in helping us to better understand the mechanisms behind genetic convergence (Li *et al*., 2020). In a study focused on cataloging worldwide detections of resistance profiles in vibrios, it was possible to observe that most of the isolated species have resistance to the classes of b-lactam antibiotics, aminoglycosides, tetracyclines, sulphonamides, chylonones and macrolides (Kumarage; De Silva; Heo, 2022). These classes were also the most detected by the studies analyzed herein (**Fig**.6).

Another important group of genes that are still poorly studied along the Brazilian coast thought directly related to one of the major concerns about AMR were the multidrug resistance genes (MDR) and adaptive changes in bacterial efflux pumps (EPM), which can result in resistance to antibiotics and other compounds such as detergents (Piddock, 2006). There are 5 families of genes that form membrane proteins responsible for MDR and any mutation in these proteins has the potential to hinder the entry of antibiotics or alter the flow of entry and exit of compounds in the cell, reducing their retention within the cell (Piddock, 2006; Chitsaz & Brown, 2017; Vats, Kaur, & Rishi, 2022). Factors that induce the selection of bacterial populations can promote resistance, even with minimal concentrations of antibiotics, pesticides, detergents, and heavy metals, potentially selecting and stimulating HTG among bacteria, thus increasing the primary and secondary spread of these genes over the coast (Domínguez, Chacón, & Wallace, 2021; Vats, Kaur, & Rishi, 2022).

OTP genes are among the MDR-promoting genes thought yet poorly investigated, with a study detecting *acrA*, *acrB*, *mexB*, *mexF*, and *tolC* in a coastal lagoon in southeastern Brazil (Leite *et al*., 2019). Moreover, the *oqxAB* gene, frequently found in persistent infections in Brazil (Silveira *et al*., 2021), was not explored, highlighting the question about which genes particularly regarding MDR are most transferred from hospitals to coastal and marine environments. Given that the marine environment is known to accumulate ionizing molecules capable of promoting MDR genes (Yang *et al*., 2019), one should address the presence of these genes in ballast water, which may also contain high concentrations of heavy metals and chemical compounds (Feng *et al*., 2017; Vats, Kaur, & Rishi, 2022).

In addition to genes related to bacterial chromosomal DNA metabolism are part of the least explored genes on the Brazilian coast, the *GyrA* gene, associated with gyrase protein, and the *ParC* gene, related to topoisomerases, are of great medical importance. *GyrA* induces negative twists in DNA during cellular replication, while *ParC* acts at the end of replication. Mutations in these genes might generate MDR bacteria, especially against quinolones, due to the inhibition of DNA synthesis and the interaction between those enzymes (Marchese & Debbia, 2016; Arabameri *et al*., 2021). Despite the inclusion of the quinolone class into the WHO and OIE critical priority list, with ciprofloxacin as prominent (Arabameri *et al*., 2021), there are only two studies, one in Rio Grande do Sul and another in São Paulo, addressing the occurrence of these genes. This further highlights the mismatch between scientific efforts in coastal regions on resistance genes and the priorities of WHO and OIE, and therefore with the reality of genes actually found in hospital environments.

4. CONCLUSION

Scientific efforts related to antimicrobial resistance in the marine environment in Brazil have grown, considering technological advancements and the increasing concern of global governments. However, these efforts have been diffuse over the 12 years covered by this work. Most antibiogram (phenotypic) studies were not aligned with the antibiotics deemed most important by the WHO and OIE. The studies analyzed did not investigate detections of resistance genes in ballast water, which serves as an entry point for foreign-resistant microorganisms along the coast (primary introduction) but also as a pathway for secondary spread over the Brazilian coast. Regarding regional distribution, it became clear that more research is needed in port areas and river mouths, with standardized monitoring, particularly concerning sampling sources, so that they correlate with observations in both culturable and non-culturable bacteria. Furthermore, they need to be aligned with the resistance genes that are most detected in hospital environments, to unveil whether they are spread over the marine environment or confined near urbanized areas, especially those bacteria from the ESKAPE group.

Nevertheless, future studies on AMR in coastal and marine environments in Brazil would be helpful to Public Health policymakers in building a more conclusive scenario, mainly at a quantitative genetic level in waters. Finally, it is recommended the implementation of multidisciplinary research studies involving target regions to detect and measure possible disseminators, the presence and concentration of AMR in water, in organisms (biofilms), pollutants (solid waste), and in exported and imported waters such as ballast water on ships.

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