Dissemination of carmbapenemases in Gram- negative bacteria in Brazilian hospitais: A review

ABSTRACT

Antimicrobial resistance in bacteria with carbapenemase activity is a growing public health problem of global proportions. This integrative review synthesizes data from 26 scientific articles published between 2020 and 2024 to analyze the dissemination and genetic diversity of carbapenemases in Brazil. Data were retrieved from the National Library of Medicine (PubMed) and the regional portal of the Virtual Health Library (BVS). The review highlights significant regional variability in carbapenemase prevalence, with the blaKPC gene being the most frequently identified resistance mechanism across multiple Brazilian states. The identification of novel trends, including the simultaneous presence of blaNDM and blaKPC genes in isolates of Proteus mirabilis and Serratia marcescens, in addition to the observation of blaNDM in Klebsiella aerogenes, highlights the intricate nature of antimicrobial resistance patterns. The state of Pernambuco is notable for reporting the first identification of blaVIM-2 in *Acinetobacter baumannii* and the blaOXA-23-like and blaOXA-143 genes. These findings emphasize the widespread cohabitation of resistance genes, with mobile genetic elements facilitating intra- and interspecies transfer among Gram-negative bacilli. Understanding this genetic diversity is crucial for developing targeted public health interventions. The study underscores the urgent need for enhanced genomic surveillance, robust infection prevention measures, and strengthened antimicrobial stewardship programs to address the growing threat of multidrug-resistant organisms in Brazil and mitigate their impact on global health..

Keywords: Carbapenemases, Carbapenem-Resistant Enterobacteriaceae, Carbapenem Resistance, Gram-Negative Bacilli, and Brazil.

1. INTRODUCTION:

Since the late 20th century, infections caused by multidrug-resistant bacteria have become a significant global concern, recognized as a serious public health problem. These infections are often associated with treatment failures and the increased costs related to morbidity and mortality in patients, particularly those hospitalized. In addition to impacting the morbidity and mortality of diseases, bacterial resistance to antibiotics results in high hospital costs, as this resistance is frequently linked to the indiscriminate use of antibiotics [1].

Microorganism resistance to antibacterial drugs (AMR) is a serious problem that affects the global population. Annually, approximately 1.27 million individuals lose their lives as a result of bacterial resistance to antibiotics, and projections indicate that, by 2050, this number could reach 10 million deaths due to AMR. The main causes of this phenomenon are linked to the inappropriate and uncontrolled use of traditional antibiotics over decades, resulting in a serious public health challenge worldwide [2]

Carbapenems are antimicrobial drugs used in hospitals and are often the last resort for the treatment of infections caused by multidrug-resistant microorganisms (MRM). These drugs are

typically the preferred option for managing severe infections caused by enterobacteria that produce extended-spectrum β-lactamases (ESBLs) [3].

The most frequently identified groups of carbapenemases include KPC, NDM, and OXA-48, which limit the available treatment options. The rapid spread of acquired carbapenem resistance is increasingly facilitated by mobile genetic elements, such as plasmids, which transfer carbapenemase genes both within and between Gram-negative bacilli (GNB). The β-lactamase genes present in mobile genetic elements play a crucial role in the rapid global spread of antibiotic-resistant GNB [4].

Carbapenem resistance can develop due to the poor penetration of active agents, which results from genetic alterations leading to different types of porin membrane proteins and/or efflux mechanisms, in addition to the production of enzymes called carbapenemases. This latter aspect is particularly important due to the great diversity of these enzymes, especially the metallo-β-lactamases (MBLs) [5].

Carbapenemases have the ability to hydrolyze a variety of β-lactam antimicrobial agents, including carbapenems, cephalosporins, penicillins, and monobactams (such as aztreonam). These enzymes can be inhibited by clavulanic acid and tazobactam. They are classified into Ambler classes A, B, and D, with serine carbapenemases (classes A and D) and metallo-β-lactamases (class B) [6].

Metallo-β-lactamases are frequently identified in Enterobacteriaceae and Pseudomonas aeruginosa. Among MBLs, New Delhi metallo-β-lactamases (NDM), Verona integron-encoded metallo-β-lactamases (VIM), and imipenem-hydrolyzing metallo-β-lactamases (IMP) are among the most common worldwide [7].

Thus, considering the importance of multidrug-resistant bacteria in the health field and the global increase in resistance to carbapenems, which is an urgent public health problem, the results of this review are essential to understand the epidemiological trends and resistance mechanisms that are specific to Brazil. Since carbapenems are more potent drugs that need to be monitored for treatment in patients, this study helps to understand the CRO in this subject.

Synthesizing studies conducted from 2020 to 2024, the manuscript provides a synthetic view of the genetic diversity of resistance mechanisms, such as the blaKPC and blaNDM genes, and their implications for clinical practice.

2. METHODOLOGY

This is an integrative literature review based on scientific articles to analyze the resistance profile of carbapenemase-producing microorganisms in Brazil, during the period from 2020 to 2024.

The methodology applied in this study is based on synthesizing results from various sources regarding the proposed topic, aiming to gather, update, and synthesize the available scientific evidence on the subject, thereby contributing to the deepening of knowledge on the investigated theme.

The guiding question of this work was formulated by incorporating the identification of keywords to facilitate the search and guidance of the research. Thus, it was defined as: "What is the resistance profile of carbapenemase-producing Gram-negative bacilli in Brazil?"

The search was conducted in the MEDLINE (PubMed) and regional portal of the Virtual Health Library (BVS) databases, using scientific articles published between 2020 and 2024, and applying the following keywords: Carbapenemases, Carbapenem-Resistant Enterobacteriaceae, Resistant to Carbapenems, Gram-Negative Bacilli, and Brazil. Boolean operators AND and OR were used to refine the keyword search.

Those descriptors and keywords were entered in both Portuguese and English, and the selected scientific articles were in the respective languages. The established filter period was set to include studies published between 2020 and 2024 for the evaluation of the epidemiological situation of carbapenemases in Brazil. Literature reviews and other studies that did not meet the specified criteria were excluded, as well as works that did not describe the analysis of carbapenem genes resistance (Fig 1).

Data collected from the selected articles were summarized in Table 1, which was organized with the following items: article title, publication year, biological examined material, isolated microorganisms, resistance profile, and genes resistance. An Excel spreadsheet was developed for the storage and systematization of the data.

This methodology provides critical insights for researchers, healthcare professionals, and policymakers involved in formulating effective strategies to mitigate disease attributable to resistant microbial entities.

3. RESULTS

3.1. SELECTED ARTICLES

A total of 776 (PubMed) and 272 (BVS) articles were found as a result of the search, based on the descriptors used in the searched databases. After applying the inclusion and exclusion criteria, 75 articles remained. After duplicates were removed and the articles that did not align with the proposed topic were excluded, 26 articles were selected for qualitative analysis . (Fig. 1).

The selected studies were published between 2020 and 2024 and analyzed hospital infections caused by carbapenemase-producing microorganisms in Brazil.

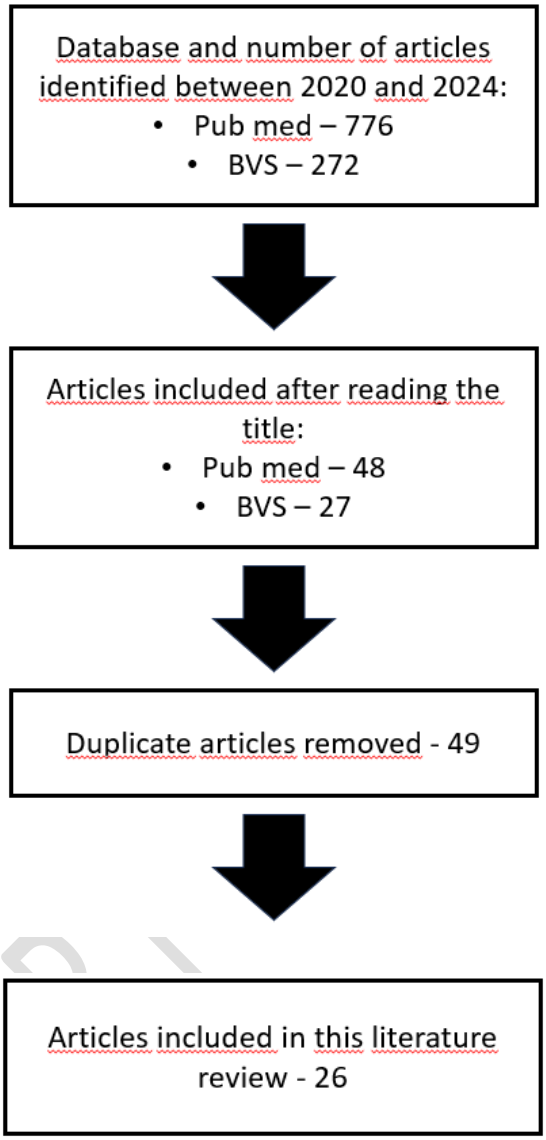

Fig 1: Flowchart of the methodological steps for article selection of inclusion in the review.

Source: Authores (2024).

Table 1: Highlighted results by study for investigation of carbapenemases dissemination in Brazil (2020-2024)

AUTHOR, YEAR OF PUBLICATION AND STATE	EXAMINED MATERIAL	MICROORGANISMS	RESISTANCE PROFILE	GENES RESISTANCE
Flores *et al*., 2020; Rio de Janeiro[10]	Rectal swabs	*Klebsiella pneumoniae*	All 11 isolates were resistant to β-lactams, 90% to ciprofloxacin, 82% to tigecycline, 73% to gentamicin and 18% to amikacin.	All presented bla_{NDM}, 27% showed co-occurrence with the $bla_{KPC,OXA-48}$ and $_{VIM}$ genes, 46% with bla_{KPC} and bla_{VIM} and 18% with bla_{VIM}.
Urzedo *et al*.,2020;Uberlândia[12]	Unspecified	*Pseudomonas aeruginosa*	ciprofloxacin (100%), gentamicin (100%) and cefepime (87.5%).	52.6% isolates presented bla_{VIM} and bla_{IMP}.
Cury *et al*., 2020; São Paulo [13]	Rectal swabs	Unspecified	Unspecified	8.4% presented the $bla\text{-}_{KPC}$ gene, 0.5% bla_{VIM}, and 0.2% bla_{NDM}.
Firmo *et al*.,2020; Pernambuco [19]	Urine (34.3%), tracheal aspirate (20.0%), blood (1%), cerebrospinal fluid (8.6%), surgical wound (5.7%), rectal swab (5.7%), bone (2.9%), lesion swab (2.9%), abscess (2.9%), sacral ulcer (2.9%) and fibrosis (2.9%)	*Klebsiella pneumoniae* (45,7%), *Proteus mirabilis* (28,6%) and *Serratia marcescens*(25,7%)	All isolates were resistant to one or more carbapenems. 17.1% of isolates were resistant to amikacin, gentamicin and tobramycin.	25.7% presented $bla_{NDM\text{-}1}$, 88.6% $bla\text{-}_{KPC\text{-}2}$, 14.3% presented these two genes concomitantly.

AUTHOR, YEAR OF PUBLICATION AND STATE	EXAMINED MATERIAL	MICROORGANISMS	RESISTANCE PROFILE	GENES RESISTANCE
Vivas *et al*.,2020; Sergipe [22]	Unspecified	*Klebsiella pneumoniae*	1.3% of the bla_{NDM} -positive isolates were susceptible to imipenem and meropenem. 14.3% of the bla_{KPC} -positive isolates were susceptible to imipenem and meropenem. 97.4% of the bla_{NDM} -positive isolates were considered susceptible to polymyxin.	One or more of the genes analyzed were detected in 56.5% of the isolates, with 50.3% harboring bla_{NDM}, 5.4% bla_{KPC}, and 1.2% bla_{NDM} and bla_{KPC}.
Santos *et al*.,2020; Pará [23]	Blood (17,2%) and urine (15,6%)	*Klebsiella pneumoniae*	12.5% were resistant to carbapenems and 81.2% were multidrug-resistant (MDR).	10.9% of the isolates tested positive for bla_{KPC-1}.
Soares *et al*., 2020;Pernambuco[18]	Unspecified	*Klebsiella aerogenes*	Sensitive to amikacin, gentamicin, tobramycin, tigecycline, colistin and polymyxin B, and susceptible, with increasing exposure (I), to ciprofloxacin, according to BrCAST.	This was the first report of the bla_{NDM} gene in clinical isolates of K. aerogenes in Brazil.
Freitas *et al*., 2020. Rio Grande do Sul [26]	Unspecified	*Acinetobacter baumannii*	95.4% and 77.3% of the isolates were resistant to meropenem and imipenem, respectively..	bla_{VIM} was identified in 90.9% of the isolates.
Junior *et al*., 2021.Pernambuco [20]	Unspecified	*Pseudomonas aeruginosa*	Unspecified	32.4% presented bla_{KPC} , 38.2% *bla*-$_{VIM}$, and one isolate presented both genes concomitantly.

AUTHOR, YEAR OF PUBLICATION AND STATE	EXAMINED MATERIAL	MICROORGANISMS	RESISTANCE PROFILE	GENES RESISTANCE
Wink *et al*., 2021. Porto Alegre[28]	Unspecified	Unspecified	Unspecified	85.8% presented the $bla_{\text{KPC-like}}$ gene and 10% $bla\text{-}_{\text{NDM-like}}$.
Stallbaum*et al*., 2021. Rio Grande do Sul[25]	Unspecified	*Klebsiella pneumoniae*	83.3% of isolates were resistant to imipenem and meropenem.	All isolates evaluated in this study presented the bla_{KPC} gene.
Higashino *et al*., 2021. São Paulo [14]	Rectal swabs	*Klebsiella pneumoniae*	Unspecified	90% presented the bla_{KPC} gene, of which 3 presented two genes concomitantly bla_{KPC} and $bla\text{-}_{\text{NDM}}$.
Souza *et al*., 2021. Mato Grosso do Sul[30]	Unspecified	*Pseudomonas aeruginosa*	100% of *P. aeruginosa* resistant to carbapenems	11% presented the $bla_{\text{KPC-2}}$ and bla_{TEM} genes, and 7% the bla_{SHV} gene.
Gollino*et al*., 2021. Rio Grande do Sul[27]	Tracheal aspirate	*Acinetobacter baumannii*	100% susceptibility to polymyxin B	94.4% of the isolates presented the $bla_{\text{OXA-23}}$ gene.
Ribeiro*et al*., 2021.Pará [24]	Tracheal aspirate (50%), blood (16.7%), postoperative wound swabs (16.7%), catheter tips (11.1%) and inguinal swabs (5.6%).	*Acinetobacter baumannii*	Isolates were resistant to almost all antimicrobials tested and remained susceptible to tigecycline and polymyxin B.	All isolate characterized as carbapenemase producers harbored the $bla_{\text{OXA-23}}$ and $bla_{\text{OXA-51}}$ genes.
Neto *et al*., 2022. (MA),(PI), (SE); (GO),(RJ), (MG), (ES), (RS) [8]	Unspecified	*Klebsiella pneumoniae*	29.5% resistant to colistin	77% presented the bla_{KPC} gene.
Freire *et al*., 2022. São Paulo [15]	Swabs retais	*Klebsiella pneumoniae*	Não Especificado	85,5% presented the bla_{KPC} gene.

AUTHOR, YEAR OF PUBLICATION AND STATE	EXAMINED MATERIAL	MICROORGANISMS	RESISTANCE PROFILE	GENES RESISTANCE
Rodrigues *et al*., 2022; Mato Grosso do Sul [29]	Unspecified	*Klebsiella pneumoniae*	Unspecified	88.9% presented the bla_{KPC} gene, 73.5% bla_{SHV}, 72.2% bla_{TEM} and 43.9% bla_{CTX-M}.
Altafini *et al*., 2022; Paraná [34]	Blood, urine, and tracheal aspirate	*Klebsiella pneumoniae*	Unspecified	75% of the isolates presented the bla_{KPC} gene, 19.2% bla_{NDM} and 5.7% presented two genes concomitantly bla_{KPC} and bla_{NDM}.
Rocha *et al*., 2022. Bahia [35]	Rectal swabs	*Klebsiella pneumoniae*	100% de resistência à colistina	94.7% presented the bla_{KPC} gene, 16.0% bla_{NDM} and 1.7% bla_{GES}.
Arend *et al*., 2023. Paraná[31]	Urine (48%), blood (14%), tracheal aspirate (16%), body fluids (4%), and other clinical specimens (18%).	*Klebsiella pneumoniae* (68,5%), *Escherichia coli* (10,1%), *Enterobacter cloacae complexo*(7,6%), *Acinetobacter baumannii* (2,2%) and *Pseudomonas aeruginosa* (0,6%).	All isolates were resistant to imipenem, 92% to amikacin, 72% were sensitive to colistin and 40% to gentamicin.	4,55% presented the bla_{NDM} gene.
Barroso *et al*., 2023. São Paulo[16]	Swab (65.4%) blood (11.5%), urine (11.6%), tracheal aspirate (3.8%), pleural fluid (3.8%), and surgical wound (3.8%)	*Klebsiella pneumoniae*	Unspecified	72.2% carried bla_{KPC}, the only carbapenemase-coding gene found.
Rocha *et al*., 2024. Pernambuco [17]	Unspecified	*Acinetobacter baumannii*	Widespread resistance to multiple antimicrobials was evident	The $bla_{OXA-23,\ 24,58\ and\ 143}$, bla_{VIM} and bla_{NDM} genes were detected. Furthermore, this is the first report of bla_{VIM-2} genes in *A. baumannii* isolates carrying the $bla_{OXA-23-like}$ gene or the $bla_{OXA-143}$ genes in Brazil.
Santos, *et al*., 2024. Rondônia [36]	Unspecified	*Acinetobacter baumannii, Klebsiella pneumoniae, Pseudomonas aeruginosa Enterobacter cloacae*	Unspecified	*A. baumannii* isolates $bla_{OXA-23-like}$ 75.2%, $bla_{OXA-58-like}$ 19% and $bla_{OXA-143-like}$ 4.1%. In *K. pneumoniae* isolates, the bla_{KPC} gene encoded the majority of carbapenemases 95.7%.

AUTHOR, YEAR OF PUBLICATION AND STATE	EXAMINED MATERIAL	MICROORGANISMS	RESISTANCE PROFILE	GENES RESISTANCE	
Krul*et al*., 2024. Paraná [32]	Unspecified	*Klebsiella pneumoniae*	Unspecified	The most frequent resistance gene was bla_{KPC}.	
Martins*et al*., 2024. Pernambuco[21]	Unspecified	*Klebsiella pneumoniae*	Unspecified	46.66% had bla_{NDM}, 35.55% bla_{KPC} and 17.79% had both genes concomitantly.	

4. DISCUSSION

A study conducted by the Hospital Infection Research Laboratory (LAPIH - FIOCRUZ) covered four regions of Brazil, including eight states: Northeast; Central-West; Southeast and South. A total of 502 clinical isolates of *Klebsiella pneumoniae* were analyzed, collected from samples of blood, urine, tracheal aspirate, rectal swab, catheter tips, sputum, tissue fragments and wounds. The investigation included resistance to polymyxins, genetic factors related to clonality, in addition to the search for genes associated with resistance to carbapenems and an assessment of antimicrobial resistance. The results of the study showed a colistin resistance rate of 29.5% in the *K. pneumoniae* samples. The bla_{KPC} gene was found in 77% of the samples, indicating high resistance to polymyxins due to their use as a treatment. Recently, the WHO classified polymyxins as "critical" antimicrobials, since they are among the few options available for the treatment of severe bacterial infections. On the other hand, the increase in resistance to carbapenems in the last decade has favored the spread of KPC, also resulting in an increase in resistance to polymyxins [8]. Further research on antimicrobial resistance in hospitalized patients need to be conducted to map the local situation. This will allow the implementation of effective and targeted actions in the area of public health to address this urgent problem [9].

Rio de Janeiro: In a study on the surveillance culture of patients hospitalized in an intensive care unit of a hospital in Rio de Janeiro, the genetic relationship of carbapenem-resistant *Klebsiella pneumoniae* carrying the bla_{NDM} gene was analyzed. The study identified that 27% of the strains showed correlation with KPC, OXA-48, and VIM, 46% with KPC and VIM, and 18% with the VIM type. None of the strains analyzed presented the resistance genes bla_{KPC}, bla_{SPM}, or bla_{IMP}. All 11 isolates demonstrated resistance to β-lactams and were classified as multidrug-resistant. The coexistence of *K. pneumoniae* producing NDM with other carbapenemases has been frequently reported in various regions worldwide. Furthermore, for the first time, it was observed that *K. pneumoniae* can harbor up to four types of carbapenemases in active surveillance cultures[10]. These findings allow us to understand how resistant clones are spread among hospital units and patients, making it possible to discover which profiles are endemic in the hospital to outline control and even therapeutic measures [11].

Minas Gerais: A study conducted in a tertiary university hospital in the city of Uberlândia, MG, in 2020, analyzed the detection of resistance genes in 138 carbapenem-resistant *Pseudomonas aeruginosa* isolates, identified as bla_{SPM}, bla_{VIM}, and bla_{IMP}, with high resistance frequencies to ciprofloxacin (100%), gentamicin (100%), and cefepime (87.5%). These results highlight a significant shift in the epidemiology of carbapenem-resistant *P. aeruginosa* isolates in a Brazilian hospital, with low detection of SPM and VIM, suggesting the involvement and coexistence of other resistance mechanisms in these strains and encouraging a reevaluation of empirical antibiotic use guidelines in institutions[12]. It is crucial to emphasize the singular importance of public health, considering the high risk of outbreaks, especially in the current

health scenario marked by the SARS-CoV-2 pandemic. Thus, the considerable number of infections caused by *P. aeruginosa* and the increase in resistance to available antimicrobials make evident the need for epidemiological research to better understand the situation in Brazil.

São Paulo: The detection of the bla_{KPC} gene in *Klebsiella pneumoniae* in three surveillance studies using rectal swab samples from various hospitals in the city of São Paulo indicates the need for the adoption of infection control strategies to minimize costs and harm to patients, particularly those undergoing transplantation or in critical health conditions[13],[14],[15]. In another study conducted in a pediatric hospital in São Paulo, where samples from different biological sites were analyzed, it was found that 72.2% of carbapenem-resistant *K. pneumoniae* isolates also carried the bla_{KPC} gene. These results highlight that the strains found in the pediatric population are similar to those detected in adults, underscoring the importance of epidemiological surveillance for the effective implementation of preventive and control measures[16].

Pernambuco: In a reference hospital located in Recife, the first case of bla_{VIM-2} in *Acinetobacter baumannii* isolates carrying the $bla_{OXA-23-like}$ gene and the $bla_{OXA-143}$ gene was recorded in Brazil. Among the 78 *A. baumannii* isolates analyzed, widespread resistance to various antimicrobials was observed[17]. Additionally, the first case of the bla_{NDM} gene in clinical isolates of *Klebsiella aerogenes* in Brazil was documented in 2020 in the state of Pernambuco[18]. A study conducted in three hospitals in Recife also reported the first case of the association between bla_{NDM-1} and bla_{KPC-2} in *Proteus mirabilis* and *Serratia marcescens* in Brazil[19].

Another study conducted in Pernambuco highlighted the analysis of clinical *P. aeruginosa* isolates, where the bla_{KPC} and bla_{VIM-2} genes were detected in 32.4% and 38.2% of the samples, respectively, with one of the isolates carrying both the bla_{KPC} and bla_{VIM-2} genes[20]. The reports of antimicrobial resistance, with the detection of the bla_{VIM-2}, bla_{NDM}, and bla_{KPC} genes in bacterial isolates in Brazil, particularly in Recife, indicate a concerning scenario of bacterial resistance. These findings underscore the urgent need for monitoring and controlling hospital infections, as well as the importance of effective antimicrobial stewardship strategies to contain the spread of these resistant strains.

A study conducted in Pernambuco, involving patients with and without COVID-19, showed that one of the main species of microorganisms identified was *Klebsiella pneumoniae*, with the detection of the resistance genes bla_{NDM} (46.66%), bla_{KPC} (35.55%), and both concurrently (17.79%). The presence of *Enterobacterales* carrying bla_{KPC} and bla_{NDM}, particularly *K. pneumoniae*, in infections and colonizations of patients with and without COVID-19, highlights the genetic diversity and carbapenem resistance observed in various species of this order[21].

The detection of the bla_{NDM} and bla_{KPC} genes in multiple hospitals (inter-hospital spread) indicates the need to adopt infection control strategies in healthcare institutions in Recife,

northeastern Brazil. This aims to reduce costs and minimize losses caused by this invasive microorganism, especially in critically ill patients [11].

Sergipe: A study conducted in a public hospital in Aracaju revealed that the majority of *Klebsiella pneumoniae* isolates (50.3%) were positive for bla_{NDM}, while 1.2% were positive for both bla_{NDM} and bla_{KPC}. Among the isolates that tested positive for bla_{NDM}, 97.4% were considered sensitive to polymyxin, and only 1.3% showed sensitivity to imipenem and meropenem. The presence of NDM has been associated with multidrug resistance and has been reported in various Brazilian states, affecting different species of Gram-negative bacteria. These findings highlight the rapid spread of NDM-positive isolates and underscore the urgent need for alternative therapies to treat infections caused by these multidrug-resistant isolates. The KPC and NDM enzymes are rarely found in the same strain, and the concurrent production of these carbapenemases in a single strain can lead to significant resistance to carbapenems[22].

Belém: A study conducted to investigate the clinical, epidemiological, and resistance-related aspects of infections caused by *Klebsiella pneumoniae* in cancer patients treated at a reference oncology center in the state of Pará identified isolates that tested positive for the bla_{KPC} gene, with 12.5% being resistant to carbapenems and 81.2% being multidrug-resistant (MDR). A high prevalence of MDR *K. pneumoniae* was observed in this study population, along with a significant occurrence of carbapenem resistance, emergence of colistin resistance, and the detection of the bla_{KPC} gene. The data obtained emphasize the need for strategies addressing epidemiological surveillance, combining continuous work between hospital infection control committees and healthcare professionals[23]. Another study conducted in a public institution in the southeastern region of the state of Pará, with kidney transplant services and renal replacement therapy, analyzed *Acinetobacter baumannii* isolates resistant to imipenem and meropenem found in different biological sites (tracheal aspirates, blood, catheter bridge), with bla_{OXA-23} and bla_{OXA-51} genes detected in all these microorganisms. Bacterial resistance is an emerging problem that demands the utmost attention and effort for mitigation. The importance of screening colonized or infected patients and providing frequent training to healthcare professionals in ICUs and clinics is emphasized. Additionally, surveillance for *A. baumannii* resistant to imipenem and meropenem, along with rational antimicrobial administration, must be reinforced[24].

Rio Grande do Sul: In an investigation conducted at a hospital in Pelotas, *Klebsiella pneumoniae* isolates associated with hospital infections were analyzed. The strains carried the bla_{KPC} gene, and 83.3% of them were resistant to carbapenems[25]. In another study, also conducted in Pelotas by Freitas et al.[26], which analyzed *Acinetobacter baumannii* strains, the researchers revealed that 95.4% of these isolates carried the bla_{VIM} gene, and 77.3% of them were resistant to meropenem and imipenem. The combination of data regarding the resistance of *K. pneumoniae* and *A. baumannii* strains in this city in Rio Grande do Sul, associated with the presence of bla_{VIM} and bla_{KPC} genes, suggests a similarity in the resistance trajectory to

carbapenems that impacts these microorganisms. These findings should serve as a call to action for joint efforts among hospitals, public health authorities, and researchers to combat the growing threat of infections caused by multidrug-resistant bacteria in hospital environments.

Additionally, the first data on the *Acinetobacter baumannii* profile in the western border of Southern Brazil raise concerns about the presence of endemic clones producing OXA-23 in this region. This study demonstrated high resistance to aminoglycosides and fluoroquinolones, contrasting with 100% sensitivity to polymyxin B. The bla_{OXA-23} gene was identified in 34 strains[27].

Furthermore, a study conducted at a tertiary hospital in Southern Brazil evaluated the growth in the frequency of bla_{NDM}, highlighting a constant increase of $bla_{NDM\text{-like}}$ genes, which rose from 4.2% in 2015 to 24% in 2020. This increase in the detection frequency of bla_{NDM} raises an important issue, as the therapeutic options available for the treatment of patients infected by bla_{NDM}-carrying bacteria are currently very limited[28].

Mato Grosso do Sul: A study conducted in Mato Grosso do Sul aimed to determine the molecular epidemiology of *Klebsiella pneumoniae* carrying bla_{KPC}, recovered from three public hospitals in Brazil. The *K. pneumoniae* isolates presented in the study carried the following resistance genes: bla_{KPC} (88.9%), bla_{SHV} (73.5%), bla_{TEM} (72.2%), and bla_{CTX-M} (43.9%). Additionally, new sequences of types that had not been previously identified in the country were detected. It was observed that *K. pneumoniae* belonging to the same clone was present in different hospitals within the same region, highlighting the spread of multidrug-resistant *K. pneumoniae* [29].

At a public tertiary hospital located in the municipality of Dourados, Mato Grosso do Sul, an evaluation of *Pseudomonas aeruginosa* isolates resistant to carbapenems was conducted, of which only 10.7% were *KPC*-producing strains. The production of carbapenemase has emerged in Brazil as the main mechanism of resistance to carbapenems among clinical isolates of *P. aeruginosa*. However, despite the identification of some *KPC*-producing strains, the low rates suggest that other mechanisms of carbapenem resistance may also be at play [30].

Paraná: A study conducted across multiple hospitals in eight cities in the Southern region of Brazil investigated the spread of bacteria producing NDM in clinical samples from urine, blood, tracheal aspirates, and body fluids. The number of isolates with bla_{NDM} in the southern cities of Brazil has been growing significantly. Moreover, the frequency varies considerably between municipalities, indicating that some cases correspond to small, localized outbreaks, while in others there is a more widespread dissemination. This situation poses challenges for treatment, as carbapenem antibiotics are the last β-lactams with proven efficacy against nearly all Gram-negative microorganisms study conducted in Paraná examined the molecular epidemiology and mechanisms of carbapenem resistance in *K. pneumoniae* isolates from

pediatric patients, identifying that the most common resistance gene found was *bla*$_{KPC}$ [31]. Preventing the spread of *K. pneumoniae* in neonatal intensive care units (ICU) is essential and requires rigorous implementation of infection control measures, including adequate hand hygiene, regular cleaning and disinfection of equipment and surfaces, and the adoption of contact precautions when dealing with colonized or infected patients. Furthermore, active epidemiological surveillance and traceability of resistant strains are crucial to identify and control outbreaks on time [32]. Both stight the occurrence of two different resistance genes, but in distinct populations: adults and children. In an additional study in the state of Paraná, in the city of Maringá, among COVID-19-infected patients who were carriers of *K. pneumoniae* producing carbapenemase, it was found that 75% of isolates carried the *bla*$_{KPC}$ gene, 19.2% harbored *bla*$_{NDM}$, and 5.7% contained both genes[33]. Given the results presented in this research, it is essential to continuously invest in training, both in the management of antimicrobials and in infection control within healthcare settings. This will ensure that, in the post-pandemic period, antimicrobial stewardship and surveillance programs remain active, thereby reducing the emergence and spread of multidrug-resistant (MDR) microorganisms.[34].

Bahia: A study conducted at a reference hospital in Salvador aimed to investigate the genetic association, antimicrobial resistance profile, and resistance mechanisms in *K. pneumoniae* isolates resistant to carbapenems and colistin (ColR-CRKP). The material analyzed consisted of rectal swab samples. The *bla*$_{KPC}$ gene was identified in 94.7% of the isolates, *bla*$_{NDM}$ in 16.0%, and *bla*$_{GES}$ in 1.7%. The *bla*$_{OXA-48}$, *bla*$_{VIM}$, and *bla*$_{IMP}$ genes were not found. The research indicates a prolonged outbreak of ColR-CRKP, suggesting the possibility of cross-transmission of *K. pneumoniae* isolates resistant to both carbapenems and colistin [35].

Rondônia: A study conducted in the southern Amazon region aimed to map the diversity of carbapenem-resistant bacteria, with an emphasis on molecular epidemiology and the analysis of genes responsible for carbapenemase production. Seventy-two species were detected showing resistance profiles to these antibiotics, of which 25 contained at least one gene encoding carbapenemases from classes A (*bla*$_{KPC\text{-like}}$), B (*bla*$_{NDM\text{-like}}$, *bla*$_{SPM\text{-like}}$, or *bla*$_{VIM\text{-like}}$), and D (*bla*$_{OXA\text{-}23\text{-like}}$, *bla*$_{OXA\text{-}24\text{-like}}$, *bla*$_{OXA\text{-}48\text{-like}}$, *bla*$_{OXA\text{-}58\text{-like}}$, or *bla*$_{OXA\text{-}143\text{-like}}$), including species such as *K. pneumoniae*, *P. aeruginosa*, *A. baumannii*, *S. marcescens*, and *Providencia* spp. These findings have the potential to contribute to scientific knowledge, providing molecular and epidemiological data that can be used in state-level bacterial resistance surveillance, as well as supporting the formulation of public health policies [36].

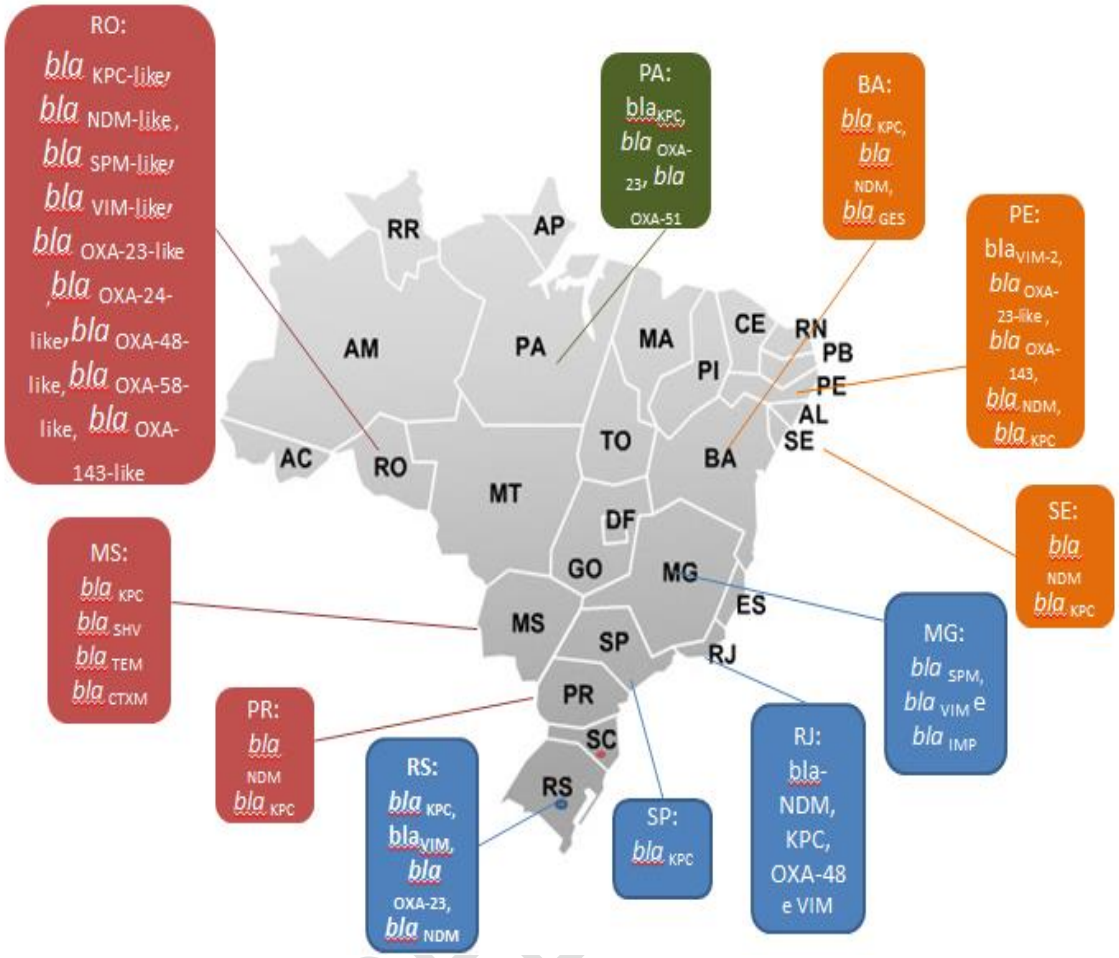

Fig 2: National patterns of gene resistance dissemination.

5. CONCLUSION

The results presented in this study highlight that the state of Pernambuco in northeastern Brazil has been significant in reporting the first case of the bla_{VIM-2} gene in *A. baumannii* isolates, along with the identification of the $bla_{OXA-23-like}$ and $bla_{OXA-143}$ genes, marking an important advancement in microbiological surveillance. Also notable is the first report of the association between bla_{NDM-1} and bla_{KPC-2} in *P. mirabilis* and *S. marcescens*, as well as the presence of the bla_{NDM} gene in *K.* aerogenes in this state.

Moreover, the cohabitation of multiple resistance genes in microorganisms isolated from several Brazilian states underscores the need for effective control and monitoring strategies, as this situation can further complicate clinical management and the efficacy of antimicrobial treatments. These findings reinforce the importance of ongoing research and the development of public health policies to address the growing threat of infections caused by multidrug-resistant bacteria in the country.

In Brazil, the complexity and diversity of bacterial resistance genes pose a significant challenge to public health. Among these genes, those that express carbapenemase and KPC stand out due to their high prevalence, contributing to resistance to last-line antibiotics. This situation is concerning, as the spread of *bla*$_{KPC}$-bearing strains can hinder the treatment of severe infections, increasing morbidity and mortality. Understanding this genetic diversity is crucial for the development of effective control and prevention strategies aimed at mitigating the impact of antimicrobial resistance in the country.

Furthermore, the manuscript emphasizes the urgent need for targeted interventions in high-risk regions in Brazil, where resistance profiles vary widely. The manuscript focuses on public health and global health security, making it a resource for framing policies and improving outcomes in regions struggling with antimicrobial resistance. The study findings are also timely given the increasing global interconnectedness that is facilitating the spread of resistant pathogens across borders.

Disclaimer (Artificial intelligence)

Option 1:

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

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