

Current global occurrence of carbapenem-resistant *Klebsiella pneumoniae* (CRKP) infections in hospitalized patients: A literature review

ABSTRACT

Antimicrobial resistance (AMR) is an escalating global issue. One of the primary resistance mechanisms is the ability of microbes to deactivate antimicrobial drugs through the production of expanded-spectrum β -lactamases enzymes (ESBL), such as carbapenemases. Among the pathogens associated with multidrug resistance, *Klebsiella pneumoniae* has a high frequency, particularly in hospital settings. This study presents a narrative review of the literature from the scientific databases of the National Library of Medicine (PubMed) and the Cochrane Library on the occurrence of carbapenem-resistant *K. pneumoniae* (CRKP) infections in hospitalized patients, identifying current studies that may contribute to understand the spread of resistant bacteria. The review was conducted in September 2023 with the aim of summarizing evidence. Inclusion and exclusion criteria were applied, and 20 articles were included, covering the continents of the America, Africa, Asia, and Europe, to select the most recent studies about CRKP. In the studies analyzed, nosocomial isolates predominantly originated from sputum samples, followed by urine and blood. Molecular analysis revealed that most microorganisms exhibiting resistance to carbapenems harbored the *bla_{KPC}*, *bla_{NDM}*, and *bla_{OXA-48}* genes. However, there is epidemiological variation among continents, underscoring the need for more knowledge about genetic diversity and the implementation of active surveillance culture programs to facilitate prompt action with appropriate therapy and minimal patient risk. These findings indicate a necessity for heightened vigilance by hospital infection control committees to prevent potential spread and outbreaks of bacteria carrying carbapenem resistance genes.

KEY WORDS: Antibiotic resistance genes; nosocomial infections; carbapenem resistance; multidrug-resistant bacteria.

• **INTRODUCTION**

Antimicrobial resistance (AMR) is experiencing a continuous escalation and has emerged as a paramount global public health concern. According to the World Health Organization [1], AMR engenders inefficacious treatments and persistent infections. The latest WHO report reveals a significant increase in high resistance levels,

particularly among bacteria accountable for sepsis within hospital environments.

Resistance acts as a defense mechanism whereby microorganisms thwart the action of antimicrobials, making antibiotics ineffective in their bacteriostatic or bactericidal effects. Consequently, bacteria proliferate despite high concentrations of drugs designed to combat them [2]. Prominent mechanisms contributing to antimicrobial resistance include the production of enzyme inactivators, alteration of antibiotic target sites, generation of efflux pumps, and modification of the permeability of bacterial cell outer membranes [3].

One of the main mechanisms of resistance is the ability of several strains to inactivate antimicrobial drugs through the production of expanded-spectrum β -lactamases enzymes (ESBL). Among them, carbapenemases are particularly notable [4]. KPC (*Klebsiella pneumoniae* carbapenemase) is a serine beta-lactamase. It can hydrolyze most beta-lactams, especially carbapenems [5]. They are the most found enzymes, especially in enterobacteria, becoming one of the most important carbapenemases since its discovery in the United States in 1996 [6].

It is responsible for the production of carbapenemases that belong to Ambler's class A serine β -lactamase K, such as: *Pneumoniae* carbapenemase (KPC), class B melato- β -lactamase (MBL) of the IMP, VIM or NDM family and beta-lactamase, which holds similarities with OXA-48 belonging to class D [7,8].

Carbapenem antibiotics possess a broad spectrum against both Gram-positive and Gram-negative bacteria, enabling resistance against degradation by most β -lactamases. Consequently, they are deemed the last option in the therapy of severe and potentially fatal infections, operating through the inhibition of cell wall synthesis and inactivation of proteins crucial for cell wall formation [9].

Among pathogens associated with diseases linked to multidrug resistance, *Klebsiella pneumoniae* is frequently detected, particularly in healthcare settings, due to its propensity to acquire and transfer genes encoding multidrug resistance mechanisms. Recognized by the WHO as a priority pathogen capable of precipitating public health emergencies due to inadequate countermeasures, *K. pneumoniae* necessitates the exploration of novel antimicrobials [10]. It is a Gram-negative bacterium prominently associated with healthcare-associated infections, primarily affecting immunocompromised patients, as an opportunistic pathogen [11].

This pathogen is implicated in various infections such as pneumonia, bloodstream infections, urinary tract infections, and surgical wound infections, often

culminating in generalized, frequently fatal, infections [12]. Resistance of *K. pneumoniae* to carbapenems in hospital settings is on the rise, particularly in intensive care units (ICUs), posing a significant public health challenge [13].

Given the multitude of factors contributing to resistance, the efficacy of specific potent drugs diminishes against multidrug-resistant microorganisms. Understanding the biochemical and genetic mechanisms related antimicrobial resistance is imperative given the substantial increase in mutations [14].

This study presents a narrative review of the literature on the occurrence of carbapenem-resistant *K. pneumoniae* (CRKP) infections in hospitalized patients, aiming to identify recent studies that could enhance comprehension of the pathogenesis of multidrug-resistant (MDR) bacteria and mitigate their dissemination.

2. METHODOLOGY

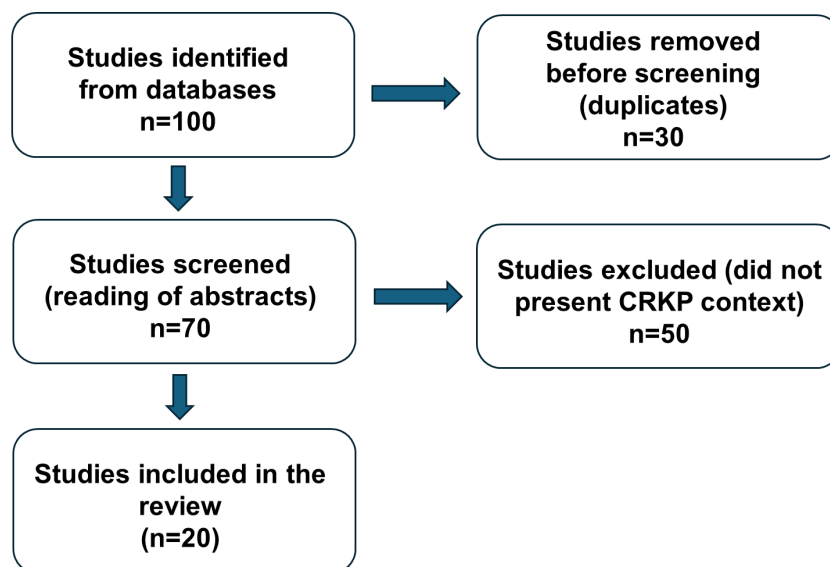
The review was conducted in the September 2023 with the aim of summarizing the most recent evidence on CRKP context. The search was performed on the MEDLINE (PubMed) and Cochrane Library databases using the following keywords: *Klebsiella pneumoniae*, carbapenem resistance, and antimicrobial resistance. The operators like AND ; OR were utilized within the keywords to enhance search performance. Articles published between 2020 and 2023 (the last four years) in either English or Portuguese were selected for analysis. Literature reviews and other studies that did not meet the specified criteria were excluded.

3. RESULTS

3.1 Selected articles

In total, 100 records were initially selected following the inclusion and exclusion criteria. After removing duplication and excluding articles that did not fit the proposed theme, there were 20 articles remaining for qualitative analysis (Figure 1).

FIGURE 1. Flowchart of the methodological steps for the selection of articles.



Source: Authors (2023).

3.2 Findings from the review

The selected studies were published in the period from 2020 to 2023 and analyzed nosocomial infections by CRKP. The studies spanned the continents of the Americas, Africa, Asia, and Europe. Next, an overview of the main findings of the studies listed for this review will be presented, divided according to their continents of origin.

3.2.1 Asia

Chen et al. [15] in China, documented isolates from different hospital sectors spanning 2017 to 2019, with a prevalence of samples originating from ICUs, primarily sputum samples. The investigation into CRKP revealed the presence of *bla*_{NDM-1} in 78.26% of the strains and *bla*_{NDM-5} in 17.39%. Ceftazidime (CZA) resistance was observed in 19.01% of cases, attributed to increased antimicrobial hydrolysis and reduced action of OmpK35.

In Iran, Zahedi et al. [16] investigated resistance to colistin in strains originating mainly from the trachea. In this case, the isolates showed molecular characteristics of *K. pneumoniae* and the genes identified in these strains were *bla_{KPC}* (58.6%), followed by *bla_{IMP}*, *bla_{VIM}*, and *bla_{OXA-48}*, with 29.0%, 14.2% and 7.4%, respectively. Furthermore, 92.6% of the strains also showed resistance to colistin, which makes the situation even more worrying, since polymyxin antibiotics are used as a last resort for the treatment of infections caused by bacteria with resistance to carbapenems, showing that resistance is growing worldwide alarmingly.

In the same period, Taha et al. [17] investigated patients with nosocomial infections at King Abdulaziz Medical City, and King Abdulaziz University Hospital in Saudi Arabia. The microorganisms responsible for these infections were isolated mainly from urine samples positive for *K. pneumoniae*, with higher frequency of the *bla_{OXA-48}* gene (79%) than the *bla_{NDM}* gene (11.7%). The results demonstrated a large increase in carbapenem-resistant Enterobacterales from 2017 to 2019 in Saudi Arabia and the predominance of the *bla_{OXA-48}* gene in this region. All strains tested showed resistance to most of the antibiotics tested, except for tigecycline and colistin.

Shen et al. [18] made a comparison between two populations in Zunyi, China, between 2018 and 2020 to determine the difference in the prevalence of carbapenemase-producing genes between children and adults. They reported prevalence of the genotypic profile *bla_{NDM}* (72.3%), followed by *bla_{KPC}* (24.5%) and *bla_{VIM}* (3.02%) among the microorganisms. In isolates positive for *bla_{NDM}*, 92.6% were from children and 7.4% from adults. Moreover, 74.3% of isolates demonstrated a MDR phenotype, and 25.7% pan-resistant or extensively resistant.

In another recent studies carried out in China and Iran, differences in genetic prevalence in relation to the expression of carbapenemases were observed. In China, Wang et al. [19] demonstrated that *K. pneumoniae* was the predominant microorganism, representing around 64.6% of isolates from nosocomial infections, with sputum as the main source, and the most found gene in these bacteria was *bla_{KPC-2}* (61.49%).

In Iran, Soltani et al. [20] analyzed CRKP isolated from several clinical samples, mainly urine, and detected a predominance of the *bla_{OXA-48}* genes (78.7%), followed by *bla_{NDM}* (19.6%) and *bla_{KPC}* (14.7%). Ghotaslou et al. [21] also conducted a survey in Iran observing several strains of CRKP isolated from urine, also detected a

higher occurrence of *bla*_{OXA-48} genes (76%), followed by *bla*_{NDM} (50%), *bla*_{IMP} (22%), *bla*_{VIM} (10 %) and *bla*_{KPC} (2%). Based on these studies, the concern with resistance developed in the hospital environment was highlighted and the need to implement preventive and educational measures among professionals was emphasized, aiming to avoid hospital infections.

In Pakistan, Gondal et al. [22] analyzed bacteria isolated from various biological samples between 2019 and 2022, most of which came from surgical wounds. The authors reported that 42.1% of them showed resistance to carbapenems, significantly related to strains of *K. pneumoniae*, and the genes in order of prevalence were: *bla*_{NDM} (41.1%), *bla*_{OXA-48} (32.6%), *bla*_{KPC} (5.5%) and *bla*_{IMP} (2.7%). Some strains harbored more than one of these genes, with the presence of *bla*_{NDM/OXA-48} (11.4%), *bla*_{OXA-48/VIM} (3.1%), and *bla*_{VIM/IMP} (0.3%) and *bla*_{OXA-48/IMP} (0.1%).

3.2.2 Europe

In Europe, research from three regions on the genetic diversity of CRKP was selected. In southern Europe, two studies stood out. Afolayan et al. [23] revealed predominance of *bla*_{KPC} (60%), *bla*_{VIM} (27%), *bla*_{NDM} (9.7%) and *bla*_{OXA-48} (2.92%) in Greece in the period from 2019 to 2023. In turn, Bovo et al. [24], in Italy, investigated the impact of the COVID-19 pandemic between 2019 and 2021, observing a greater occurrence of antimicrobial resistance due to the widespread increase in *bla*_{KPC} (75.4%), producers of *bla*_{OXA-48} (8.3%), *bla*_{VIM} (6.7%), *bla*_{KPC} and *bla*_{OXA-48} together (5.4%), and *bla*_{NDM} (4.2%). In this study, all specimens that contained *bla*_{KPC} and *bla*_{OXA-48} simultaneously were resistant to ceftazidime/avibactam, meropenem/vaborbactam, imipenem/relebactam and cefiderocol.

These authors point out that this resistance may have been linked to the presence of the gene *bla*_{OXA-48} which induces non-sensitivity to beta-lactamase inhibitors, such as vaborbactam and relebactam, while resistance to ceftazidime/avibactam is linked to mutations in the gene *bla*_{KPC3}, causing changes in its structure making the action of antimicrobials difficult.

In Central Europe, Nordmann et al. [25] evaluated strains producing carbapenemases and sensitive to ceftazidime/avibactam, meropenem/vaborbactam and imipenem/relebactam in isolates collected in Switzerland between 2018 and 2020. They found that 40.3% of specimens were from *K. pneumoniae* and 35.3% *E. coli*.

Regarding the presence of the genes *bla*_{KPC} (32%), *bla*_{OXA-48} (32%) and *bla*_{NDM} (24%), identified in *K. pneumoniae*, they observed that meropenem/vaborbactam were more effective against enterobacteria that produce carbapenemases.

In Eastern Europe, from 2017 to 2019, Fischer et al. [26] detected a higher prevalence of resistant microorganisms in urine samples from ICUs patients in Romania. In 47 *K. pneumoniae* isolates analyzed, the frequency of *bla*_{OXA-48} and *bla*_{KPC} genes were 15% and 18%, respectively.

Sarowska et al. [27] carried out microbiological identification of samples from blood in a hospital in Poland in 2020, identifying 4.4% of the microorganisms as *K. pneumoniae*. Of these, 50% were resistant to carbapenems, with 82.1% harboring *bla*_{NDM}, 14.3% producing *bla*_{VIM} and one isolate with *bla*_{NDM} together with *bla*_{OXA-48}. The tests demonstrated that in Poland, resistance to carbapenems has been increasing, indicating the importance of testing hospitalized patients to prevent or control possible outbreaks.

3.2.3 Africa

In Northern Africa two studies in Egypt were analyzed. The first was Baraka et al. [28], who in 2019 carried out molecular detection mainly from sputum and found specimens with at least two carbapenem resistance genes. All tested isolates contained the *bla*_{OXA} genes, with presence of *bla*_{VIM} (93%), *bla*_{NDM} (85.5%) and *bla*_{IMP} (63%) and, to a lesser extent, *bla*_{KPC} gene (17%).

The other study, carried out by El-kady et al. [29] in the period from 2020 to 2021, investigated strains of *K. pneumoniae* from cancer patients, also in Egypt, and detected the genes *bla*_{KPC} (42.6%), *bla*_{OXA-48} (23.4%), *bla*_{OXA-48/NDM} (10.6%) and *bla*_{IMP} (2.1%). These strains were mostly isolated from blood samples. The minimum inhibitory concentration of ceftazidime (CZA) demonstrated that 25.5% of the species analyzed were resistant to this antibiotic, a fact the authors attributed to mutations in the gene *bla*_{KPC}, along with overexpression and modification of outer membrane proteins.

According to the study, a high level of resistance to CZA was seen in both studies, which can be attributed to the incorrect empirical use of antibiotics, together with the lack of molecular analyses of the isolates.

In West Africa, in seven tertiary hospitals in Nigeria between 2018 and 2019, Odewale et al. [30] found *K. pneumoniae* (30.5%) in most urine samples. The

carbapenem resistance gene with greatest prevalence in these specimens was *bla_{VIM}* (43.0%), followed by *bla_{OXA-48}* (28.95%), *bla_{IMP}* (22.7%), *bla_{NDM}* (17.25%) and *bla_{KPC}* (13.3%). The resistance found in these nosocomial samples may have been related to inefficient practices in controlling hospital infections.

3.2.4 Americas

In South America, specifically in Brazil, Flores et al. [31] reported that 16% of strains isolated from rectal swabs from ICUs patients in Rio de Janeiro, from 2016 to 2017, were phenotypically identified as carbapenemase producers. Of these, 11% had *bla_{NDM}* gene, among these, 27% revealed co-occurrence with *bla_{KPC}*, *bla_{OXA-48}*, and *bla_{VIM}*, 46% with *bla_{KPC}* and *bla_{VIM}*, and 18% with *bla_{VIM}*.

In other study, Vivas et al. [32] analyzed *K. pneumoniae* in public hospitals in Sergipe, Brazil, finding presence of the genes *bla_{NDM}* (74%), *bla_{KPC}* (8%), in addition to *bla_{NDM}* and *bla_{KPC}* together (1.2%). Combined drug therapy of two or three treatment options was tested, with the combinations of polymyxin B with amikacin and polymyxin B with meropenem, presenting the most satisfactory responses for the isolates tested. For those authors, in clinical practice, empirical antimicrobial treatment should be considered, since delaying therapy can lead to unfavorable clinical outcomes in patients with compromised immunity.

Kiffer et al. [33] analyzed the impact of COVID-19 on carbapenemases genes in Brazil, in the period from 2015 to 2022, finding an increase in the frequency of *bla_{NDM}* from 4.1% in 2015 to 39.4% in 2022, and a decrease of *bla_{KPC}* from 74.5% to 55.1% in the same period. According to the authors, the decrease in the KPC enzyme may be related to the use in hospitals of faster resistance detection techniques, thus speeding up diagnosis and treatment. Thus, the epidemiology of these enzymes may also be changing in Brazil.

Estabrook et al. [34] described the frequency of enterobacteria non-sensitive to meropenem in a surveillance study between 2018 and 2019 in North America, Asia, and the Pacific. Most isolates were *K. pneumoniae* (71.5%). There was variation by region in relation to carbapenemases, with metallo-beta-lactamase's dominant in Africa, the Middle East (49%), and Asia/Pacific (59.4%). The gene *bla_{OXA-48}* was predominant in Europe (30%), while in Latin America, *bla_{KPC}* was most present, with 51.9%. Meanwhile, in North America the presence of this gene was 53.6%.

3.3 Qualitative analysis of studies

Table 1 presents the studies analyzed in this review, as well as some of the demographic profile of the research participants. Overall, there was a predominance of males (72.73%), with the vast majority experiencing CRKP infections associated with respiratory issues or compromised patient immunity. Among female patients (27.27%), urinary infections were the primary concern.

Most patients, with an average age exceeding 50 years, were immunocompromised and admitted to ICUs. These characteristics pose as risk factors for infections caused by MDR pathogens.

Table 1. Demographic profile of participants in each study analyzed in this review.

	Author (Year)	Gender (%)	Average Age (Years old)
1	Flores et al. (2020) [31]	n/d*	n/d
2	Vivas et al. (2020) [32]	n/d	n/d
3	Chen et al. (2022) [15]	M-84/F-37**	72.54
4	Fischer et al. (2022) [26]	M-30/F-18	58.50
5	El-Kady et al. (2022) [29]	M-46/F-88	45.56
6	Soltani et al. (2022) [20]	M-28/F-33	56.70
7	Sarowska et al. (2022) [27]	n/d	n/d
8	Odewale et al. (2023) [30]	M- 59 /F-69	n/d
9	Shen et al. (2023) [18]	M-57/F-37	n/d
10	Zahedi et al. (2023) [16]	M-94/F-68	67.25
11	Baraka et al. (2023) [28]	n/d	n/d
12	Estabrook et al. (2023) [34]	n/d	n/d

1 3	Ghotaslou et al. (2023) [21]	M-30/F-20	58.00
1 4	Gondal et al. (2023) [22]	M-1288/882	n/d
1 5	Nordmann et al. (2023) [25]	n/d	n/d
1 6	Taha et al. (2023) [17]	M-109/F-71	62.80
1 7	Wang et al. (2023) [19]	n/d	n/d
1 8	Kiffer et al. (2023) [33]	n/d	n/d
1 9	Afolayan et al. (2023) [23]	M-129/F-82	50.00
2 0	Bovo et al. (2023) [24]	n/d	n/d

* n/d: No data; ** M: Male; F: Female.

Source: Authors (2023).

The resistance genes diversity, as indicated in Table 2, illustrates the variations that can arise across different regions of the globe. Most publications concerning carbapenem resistance originate from various regions of Asia, including East, South, and the Middle East Asia. Such diversity may stem from factors such as environmental conditions, duration of hospitalization, medications administered, and protocols followed by healthcare professionals within the hospital setting.

Table 2. Characterization of the studies on nosocomial CRKP infections included in this review.

	Author (year)	Country: Region	Population	Number of CRKP- infected patients	Resistance Genes (<i>bla</i>)
1	Flores et al. (2020) [31]	Brazil: Rio de Janeiro	4,463	103	NDM, KPC, OXA-48, VIM

2	Vivas et al. (2020) [32]	Brazil: Sergipe	147	83	NDM-1, KPC
3	Chen et al. (2022) [15]	China	121	23	NDM-1, NDM-5
4	Fischer et al. (2022) [26]	Romania: Clyj Napoca	75	27	OXA-48, KPC
5	El-Kady et al. (2022) [29]	Egypt: Mansoura	350	134	KPC, OXA- 48, NDM, IMP
6	Soltani et al. (2022) [20]	Iran: Tabriz	468	61	OXA 48, KPC, NDM
7	Sarowska et al. (2022) [27]	Poland: Wrocław	115	58	NDM, VIM, OXA-48
8	Odewale et al. (2023) [30]	Nigeria	420	128	VIM, OXA, IMP, NDM, KPC, CMY, FOX
9	Shen et al.; 2023 [18]	China: Zunyi	94	94	NDM, KPC, VIM
10	Zahedi et al. (2023) [16]	Iran	162	162	KPC, IMP, VIM, OXA- 48
11	Baraka et al. (2023) [28]	Egypt: El- Behira	100	80	OXA, VIM, NDM, IPM
12	Estabrook et al. (2023) [34]	North America/ Asia/ Pacific	2,228	1.592	KPC, OXA- 48, NDM
13	Ghotaslou et al. (2023) [21]	Iran: Tabriz	87	50	OXA-48, NDM, IMP, VIM, KPC
14	Gondal et al. (2023) [22]	Pakistan: Lahore	789	283	NDM, OXA-48, KPC, VIM, IMP
15	Nordmann et al. (2023) [25]	Switzerland	150	61	KPC, OXA- 48, NDM
16	Taha et al. (2023) [17]	Saudi Arabia: Jeddah	187	180	OXA-48, NDM

17	Wang et al. (2023) [19]	China: Shanghai	161	104	KPC-2
18	Kiffer et al. (2023) [33]	Brazil	169,320	41,301	KPC, NDM
19	Afolayan et al. (2023) [23]	Greece: Athens	392	205	KPC, VIM
20	Bovo et al. (2023) [24]	Italy: Bologna	56,091	957	KPC, OXA-48

Source: Authors (2023).

In the articles analyzed, the isolates came from various types of biological samples from hospitalized patients, with predominance of sputum, followed by urine and blood. The Figure 2 displays information about the main collection sites of CRKP isolates. It is important to highlight that this microorganism can be found in various sites of the human microbiota, and can cause various damages to the human body, resulting in pneumonia, urinary tract infections, bloodstream infections and meningitis [35].

FIGURE 2. Main collection sites of CRKP isolates in the revised studies.

Source: Authors (2023).

Molecular analyses of the selected articles revealed that the most prevalent carbapenem resistance genes were *bla*_{KPC}, *bla*_{NDM} and *bla*_{OXA-48}, as demonstrated in Figure 3. It was noted that in East Asia, studies carried out in a different time frame demonstrated a gene change from *bla*_{NDM} to *bla*_{KPC}. In the East Asia, there was a change from *bla*_{NDM} to *bla*_{OXA-48}. However, in South Asia, studies have demonstrated continued prevalence of *bla*_{NDM}.

In Mediterranean Europe, studies have shown that the *bla*_{KPC} gene remains predominant, while in Western Europe there have been changes from *bla*_{OXA-48} to *bla*_{NDM}, with prevalence of *bla*_{KPC} and *bla*_{OXA-48} over *bla*_{NDM}.

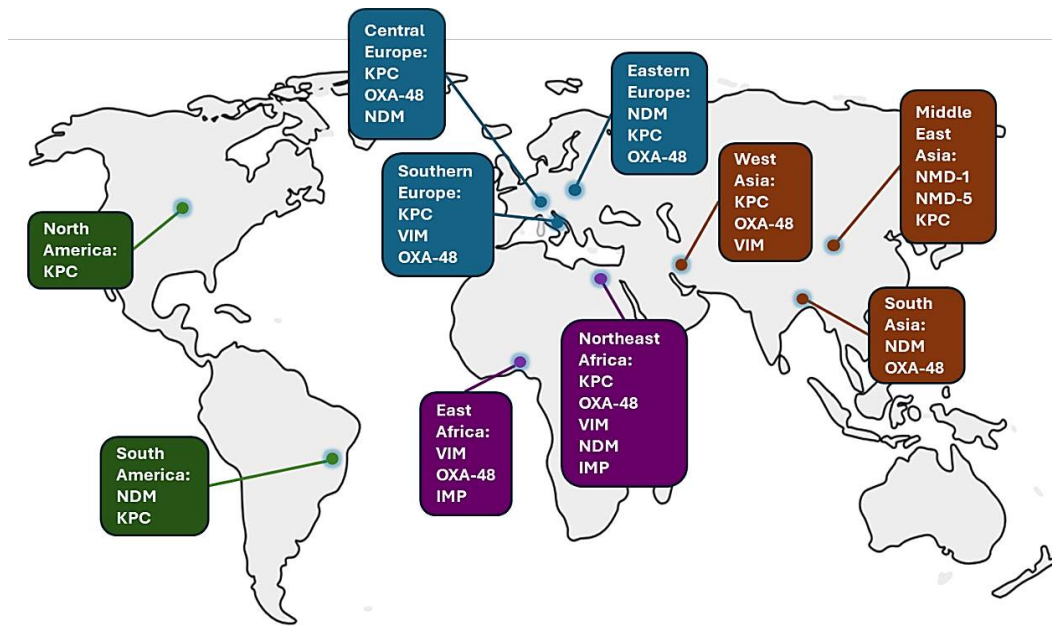
In Northern Africa there has been an increase in *bla*_{KPC} while in West Africa *bla*_{VIM} is most prevalent. In the Americas, large increases have been reported in *bla*_{NDM}, especially in Brazil, where Kiffer et al. [33] reported an increase of 39.1% in a period of five years and found decrease in *bla*_{KPC} of 19.4%.

FIGURE 3. Prevalence relative of carbapenem resistance genes in *K. pneumoniae* described in the revised studies (1-20, according to table 2).

Source: Authors (2023).

Carbapenem resistance among *K. pneumoniae* in recent years has occurred due to transmissible carbapenemase genes such as *bla_{KPC}* and *bla_{NDM}*, which have been detected with large increases, suggesting a worldwide trend. According to Nordmann et al. [25], the producers of NDM carry other types of resistance, such as ESBLs (mainly CTX-M 15) and other carbapenemases (OXA-48, VIM and KPC), which gives these strains their multi-resistance characteristics. The distribution of key resistance genes worldwide, as reported in revised studies from 2020 to 2023, is visualized in Figure 4.

Figure 4. Global dissemination patterns of primary carbapenem resistance genes in *K. pneumoniae*: insights from revised studies (2020-2023).



Source: Authors (2023).

4. Conclusion

The findings summarized here indicate an epidemiological variation of the hospital infections caused by *K. pneumoniae* among the continents, represented both by regional characteristics and by changes that have occurred in the same location. The difference among the types of resistance genes spread across the globe was also noticed. This emphasizes the imperative of garnering deeper insights into the spectrum of carbapenem resistance genes prevalent in each region and implementing structured surveillance programs for ongoing monitoring.

Such measures will facilitate prompt interventions, ensuring the administration of appropriate therapies and mitigating further risks to the health of immunocompromised patients grappling with infections. Enhanced vigilance and infection control protocols within hospital settings are indispensable to curb the

dissemination of infections, particularly amidst bustling environments, thereby averting outbreaks of multidrug-resistant microorganisms.

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