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THE PREVALENCE OF CARBAPENEM-RESISTANT ENTEROBACTERIACEAE INFECTIONS IN HOSPITALIZED PATIENTS AT INKOSI ALBERT LUTHULI CENTRAL HOSPITAL: A RETROSPECTIVE COHORT STUDY IN DURBAN, SOUTH AFRICA.

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Abstract

Introduction

Carbapenems are antibiotics that fall within the beta-lactam antibiotic family utilized against multidrug-resistant Gram-negative microorganisms due to their broad range of antimicrobial action. However, there has been a rise of carbapenemase-producing organisms that are resistant to carbapenems making the treatment of infections difficult.

Aims and Objectives

The primary aim of this research is to investigate the occurrence of carbapenem-resistant *Enterobacteriaceae* (CRE) infections among patients receiving hospital care in Durban, South Africa, and also ascertain the predominant organisms causing these infections and evaluate the efficacy of available treatment options.

Methodology

This was a quantitative, retrospective cohort study that investigated carbapenem-resistant *Enterobacteriaceae among* 534 patients of all genders and age groups. The procedure involved detecting microorganisms in a patient's blood and their susceptibility patterns. Data, spanning from January 1, 2021, to December 31, 2021, was retrospectively collected through medical laboratory reports.

Results

Results showed a total of 21.8% of cases were resistant to at least one of the three carbapenems (ertapenem, imipenem, or meropenem), with *Klebsiella spp.* This is the most prevalent (62.7%), followed by *Enterobacter spp.*(18.9%) and *Escherichia coli* (10.8%). Furthermore, the results showed that there was no significant difference between ertapenem and imipenem in terms of their efficacy against CRE. However, meropenem demonstrated the maximum effectiveness against CRE.

Conclusion

Klebsiella spp. Emerged as the predominant microorganisms, followed by Enterobacter spp. and Escherichia coli. Evaluating the effectiveness of antimicrobial drugs revealed that meropenem consistently demonstrated superior efficacy, particularly against *Klebsiella spp.* and*Enterobacter spp*., with imipenem also showing notable effectiveness, especially against *Escherichia coli*.

Recommendations

These include optimizing antimicrobial use through careful prescribing, providing education and training for healthcare personnel, expanding resistance surveillance, and fostering collaboration and data sharing among healthcare facilities to address the local and global challenges of CRE infections.

Keywords: *carbapenems, carbapenem-resistant* Enterobacteriaceae *(CRE), carbapenemases, metallo-beta-lactamases*
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Introduction

Introduction to Carbapenemases and their Mechanism of Action

Carbapenems are antimicrobial agents from the subclass of beta-lactam antibiotics that have a beta-lactam ring chemical structure that exhibits a broad spectrum of antimicrobial activity by targeting various microorganisms, even those that are resistant to other antibiotics (Codjoe and Donkor, 2017). This means that they work against a variety of microorganisms, even those that are resistant to many other

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antibiotics. Carbapenems function by preventing the synthesis of bacterial cell walls. The cell wall of microorganisms serves as a protective and supportive structural barrier and is made up of peptidoglycan (Kheyrodin*et al.*, 2022). Penicillin-binding proteins (PBPs) oversee the peptidoglycan strands' cross-linking, which is crucial for the consistency and durability of the bacterial cell wall (Egan *et al.*, 2017). Carbapenems hinder the development of a functioning cell wall by blocking PBPs, which cause bacterial cell lysis and death (PubMed, 2010). However, there has been a rise in carbapenem-resistant *Enterobacteriaceae*(CRE) through their ability to produce carbapenemase enzymes that degrade carbapenems and hinder their efficacy in killing microorganisms (NICD, 2022). This study discovered that microorganisms could bypass the antibiotic's mechanism of action and survive in its presence because they could produce enzymes required to break down carbapenems. As carbapenems have been frequently regarded as last-line antibiotics for serious infections, this has presented a substantial difficulty in the treatment of diseases brought on by these resistant microorganisms (Hasan *et al.*, 2021).

Classes of Carbapenemases and Their Impact

Carbapenemases are enzymes that fall into three molecular classes: classes A, B, and D beta-lactamases, as shown in Table 1 (Queenan and Bush, 2007). These classes include various types of carbapenemases such as metallo-beta-lactamases (MBLs) like NDM-1 and VIM, KPCs, and GESs belonging to class A, and oxacillinase-type carbapenemases such as OXA-48 and its derivatives under class D (Brink *et al.*, 2012). After a thorough review of relevant literature, this study identified KPCs and NDM-1s as the most identified CREs in hospital settings (Mitgang *et al.*, 2018). KPC and NDM-1 strains had limited treatment options, leading to increased morbidity and mortality rates among infected patients. Studies have also shown that these CREs are frequently associated with bloodstream infections, urinary tract infections, and ventilator-associated pneumonia (Kumarasamy *et al.*, 2010; Tumbarello *et al.*, 2012). As a result, the global emergence of CREs has posed a significant challenge in treating infected patients caused by these organisms, leading to increased morbidity and mortality rates. Therefore, it was important to understand the different classes of carbapenemases to develop effective interventions against these resistant microorganisms.

Table 1: Classification and characteristics of major carbapenemases in Enterobacteriaceae

Molecular Class	Carbapenemase	Common organism
A	KPC, GES	*Klebsiella pneumoniae*
B	Metallo-beta-lactamases	*Escherichia coli, Enterobacter spp., Providencia, Proteus mirabilis, Citrobacter*
D	OXA-48	*Klebsiella pneumoniae, Escherichia coli*

Numerous publications in the field of epidemiology have examined the prevalence and incidence of carbapenem-resistant *Enterobacteriaceae*(CRE). In the progression of this study, a review was done on a study conducted in one of the seven metropolitan areas in the United States that reported an incidence rate of 2.93 per 100,000 people (Guh *et al.*, 2015). This incidence rate indicated an alarming prevalence of CRE infections. However, the impact of CRE on public health has not been limited to incidence rates alone but has also increased healthcare costs and mortality rates. According to the Centres for Disease Control and Prevention (CDC) (2019), CRE caused 13,100 infections and 1,100 estimated fatalities among hospitalized patients in the United States in 2019, highlighting the importance of preventing and controlling CRE infections.

Factors Contributing to the Emergence and Spread of CRE

Furthermore, a cross-observational study conducted by Villegas *et al.* (2016) across seven Latin American countries (Peru, Colombia, Guatemala, Argentina, Mexico, Ecuador, and Venezuela) reported that CRE was present in 21% of patients with bloodstream infections caused by *Enterobacteriaceae*. This highlighted the global concern regarding the epidemiology of CRE and the need for international collaboration in developing effective strategies for controlling its spread. In South Africa, vulnerable groups like the elderly, people with chronic illnesses, and immunocompromised people were also affected by CRE infections. High mortality was observed in these vulnerable groups due to their weak immune systems. This added pressure to an already troubled public health system in South Africa. This included long hospital

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stays and inadequate treatment of CRE infections. In this current research study, I gathered valuable information regarding the use of antibiotics prescribed for patients with CREs.

This study also established that the epidemiology of CREs was a result of multiple factors, such as the widespread use of antibiotics, a lack of infection control measures, and the international movement of people and goods. In particular, the widespread use of antibiotics resulted in the selection of microorganisms that contained carbapenemase enzymes, which inactivated the antibiotic and rendered it ineffective against the CRE infection (Nordmann *et al.*, 2011). Therefore, a multifaceted approach has been required to address this public health threat, such as the development of new antibiotics, improved infection control measures, and enhanced surveillance and monitoring systems (Livermore, 2012). In Europe, as of 2012, Greece, Italy, and Turkey had the highest prevalence of CRE, whereas the Nordic countries, such as Denmark, Finland, Iceland, Norway, and Sweden, had the lowest prevalence (Cantón *et al.*, 2012). The variation in the prevalence was due to several different intervention procedures, which included antimicrobial use, the implementation of infection control measures, and the importation of carbapenemases from other foreign countries (Nordmann *et al.*, 2011; Pitout, 2010).

In contrast, recent data from South Asia and Southeast Asia indicated that carbapenem-resistant *Enterobacteriaceae*(CRE) infections had significant rates of resistance to treatment (Malchione *et al.*, 2019; Hsu *et al.*, 2017). This meant that many CRE clinical samples were resistant to carbapenem antibiotics, which are vital for treating severe infections. In other words, South Asia and Southeast Asia faced a high mortality rate due to CRE resistance to treatment. The prevalence of CRE in these regions, as shown in Figure 1, was attributed to a variety of factors, such as the overprescription of antibiotics, an overburdened healthcare system, and the international movement of people.

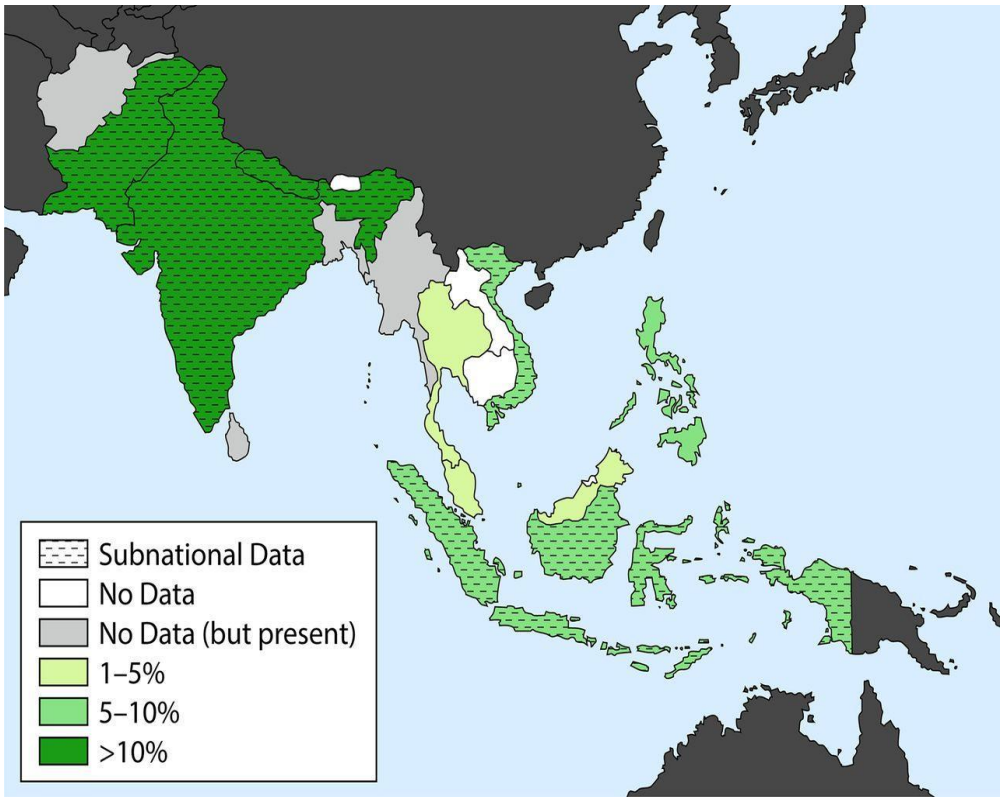

Figure 1: Estimated prevalence of CRE in South and Southeast Asian countries (Hsu et al., 2017)

In addition, inadequate environmental hygiene and sanitation were also identified in this study as contributing factors in the emergence of CRE in the communities of India, Pakistan, and Vietnam (Hsu *et al.*, 2017). In South

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Africa, particularly in the rural areas of Kwa-Zulu Natal, people also faced the same situation of hygiene and sanitation problems (Narsai, 2013). South Africa is a developing country with poor sanitation and infrastructure, which normally gives rise to oral-fecal infections. Oral fecal infections are always associated with the rise of CREs. Furthermore, the spread of CRE in these regions was a significant public health concern, given the high population densities and inadequate infection control measures. In some regions in India, CRE infections were documented in both hospital and community settings, with a reported prevalence rate of up to 32% (Bhattacharya *et al.*, 2016). Similarly, in Pakistan, CRE was identified as a significant healthcare-associated infection, with reported prevalence rates ranging from 7.8% to 51.7% (Khan *et al.*, 2019). The emergence of CRE in these regions highlighted the urgent need for effective infection control measures and improved antimicrobial treatment to prevent the further spread of this public health threat.

Challenges and Prevalence of CRE in Africa

As this study progressed, it was discovered that the distribution and prevalence of carbapenem-resistant *Enterobacteriaceae* (CRE) in Africa had not been an area of concern due to the limited documentation and understanding of these types of infections. A systematic review conducted in 2015 shed light on the scarcity of data regarding carbapenemase-producing *Escherichia coli* and *Klebsiella pneumonia,* with reports being retrieved from only 7 out of 47 nations in the World Health Organization (WHO) Africa Region (Manenzhe *et al.*, 2015). The review also highlighted that North Africa accounted for most studies identifying carbapenemase-producing microorganisms (74%), followed by Southern Africa (12%), West Africa (8%), and East Africa (6%), with South Africa having the highest prevalence rate (90%) in Southern Africa. The public health sector has been faced with challenges posed by the rapid spread of CRE infections because of several factors such as a lack of adequate infection control and, the absence of comprehensive information on CRE infections especially in Africa(Gulumbe and Ajibola, 2020). This means more research studies need to be conducted and develop interventions to curb the spread of these infections.

Due to the increasing death rates of patients admitted to hospitals because of CRE infections in Africa, has prompted an urgent need for expanded CRE surveillance, research, and infection control strategies. Furthermore, in many African countries, it was discovered that few effective drugs were available to treat CRE infections (Tompkins *et al.*, 2021). As a result, more comprehensive research is required in Africa to understand better the frequency and distribution of CRE to develop effective control as well as preventative strategies. This research study will help discover information on the availability of sufficient antibiotics for the treatment of CREs.

The Emergence of CRE in South Africa

Throughout this research, the focus shifted from the world's perspective and Africa's perspective to the Republic of South Africa. In 2011, the province of Gauteng in South Africa saw the first occurrence of carbapenem-resistant *Enterobacteriaceae* (CRE) invasive infections, specifically the KPCs and NDM-1 (Brink *et al.*, 2012). Both cases were reported to have been contracted within hospital settings, and both resulted in the unfortunate deaths of two adult patients. Since then, the incidence of CRE infections has been steadily increasing across South Africa, with the highest levels of carbapenem resistance observed in KwaZulu-Natal (KZN) and Gauteng, followed by the Eastern Cape and Western Cape, as demonstrated in Figure 2 (Sekyere, 2016).

Figure 2: A map displaying the density, distribution, and resistance mechanisms for carbapenem, colistin, and tigecycline documented thus far in South Africa. (Sekyere, 2016)

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Despite the limited documentation of CREs as mentioned earlier in this study, it was determined that CRE infections have led to an annual hospital mortality rate of 38% in South Africa (Perovic *et al.*, 2020). This has been a severe blow to the already troubled healthcare system in South Africa. South Africa's political past has resulted in major gaps, harming the health of its primarily black African people. Despite government efforts, progress toward the Millennium Development Goals has been slow. The under-resourced public health sector has faced urban-rural gaps, a quadrupling of disease burdens, and an expanding tuberculosis epidemic (Delobelle, 2013). As a result, the addition of CRE infections to the list has been extremely damaging. Therefore, this present study aimed to investigate the prevalence of CRE infections among hospitalized patients in Durban, South Africa, as part of the analysis of the effect of CRE infections in South Africa.

Prevalence of Carbapenem-resistant *Enterobacteriaceae* Infections in KwaZulu-Natal, South Africa

Since the year 2000 to date, CRE infections in South Africa have gradually increased, with Gauteng and KZN provinces at the forefront in terms of the rise of infection numbers (Seykere, 2016). The first cases of NDM-1 and KPC in South Africa were reported from clinical isolates of *Klebsiella pneumoniae* in a hospitalized patient in Johannesburg and *Enterobacter cloacae* in a hospitalized patient in Pretoria, respectively (Brink *et al.*, 2012). During the same period, the emergence of the broad-spectrum antibiotic-inactivating enzyme, OXA-48, and its derivatives among *Enterobacteriaceae was* also confirmed in hospitalized patients in Port Elizabeth, Cape Town, and Johannesburg (Brink et al, 2012).

As this study progressed, it was found that the first documented report of NDM-1 in KZN was in 2012, from a woman who had been hospitalized in India from the 21st to the 24th of October for the management of a fractured femur (Govind *et al.*, 2013). Upon her arrival at the general practitioner's office for medical examination, she had a urinary catheter which is a known risk factor for CRE infection transmissions. Other risk factors include assisted ventilation, prolonged hospital stays, prior antibiotic use, and previous hospitalization (Demir *et al.*, 2008; Andriatahina *et al.*, 2010).

Given all of this, the public healthcare system in KZN took a severe hit from the antibiotic resistance of these isolates. Since these microorganisms had been difficult to treat and had gone unnoticed, especially in South Africa's many public hospitals, the risk of epidemics remained a threat (Jacobson *et al.*, 2012). Additionally, comorbidity, such as immunocompromised people, places indirect costs on the healthcare system as they are more susceptible to infections and complications, which can lead to frequent hospitalizations, emergency room visits, and outpatient appointments. In this case, most immunocompromised individuals lived in KZN (Kharsany, 2020). Infections such as HIV, diabetes, tuberculosis, and pneumonia, which have a direct link with CRE, lead to high mortality, especially in patients admitted to hospitals for a longer period (Krishinchand, 2021). Considering the above research investigation, this study investigated the prevalence of CRE infection in both healthy and immunocompromised individuals at Inkosi Albert Luthuli Central Hospital.

Impact of CRE on South African Healthcare Systems

Carbapenem-resistant Enterobacteriaceae (CRE) has had a considerable impact on the South African healthcare system. This has been indicated by the highly disturbing CRE infection fatality rates of approximately 38% in South African hospitals (Perovic *et al.*, 2020). This shocking mortality rate has emphasized the critical need for developing an effective CRE therapy. In addition to the loss of human life, CRE infections have also placed significant financial pressure on South Africa's healthcare system. The yearly economic cost of CRE in South Africa reached over ZAR 139 million (USD 9.8 million) in the year 2019. These costs included extended hospital stays, increased antibiotic use, and infection control measures, which placed a significant strain on limited healthcare resources (Delobelle, 2013). Therefore, this high healthcare system expenditure has signaled the importance of focused investment and resource allocation in successfully combating CRE.

On the other hand, South African medical practitioners have encountered difficulty controlling CRE infections due to limited access to diagnostic facilities as well as delays in obtaining correct laboratory results, which hinder the timeous detection and treatment of CRE infections. Moreover, the lack of effective CRE antibiotics has also complicated the therapy scenario for medical practitioners as there has been a development of further antibiotic resistance. Notably, CRE infections have had a significant impact on South African healthcare systems. The high mortality rates, the country's poor economic growth, and other challenges in the general healthcare system require a diversified strategy for addressing these critical public health issues. This study will help acquire different techniques across the board that have been employed to combat CRE infections and then combine the pros and cons to develop an efficient strategy.

Therapeutic Options

An antibiotic called carbapenem, a beta-lactam, prevents penicillin-binding proteins called transpeptidases from working and blocks the formation of peptidoglycans, ultimately causing apoptotic cell death (Kohanski *et al.*, 2010). (Munoz-Price *et al.*, 2013; Tamma and Simner, 2018; Tzouvelekis *et al.*, 2012; Goodman *et al.*, 2016) found that CRE resistance to carbapenems is frequently caused by the synthesis of carbapenemase or a combination

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of structural changes and the emergence of additional beta-lactamases, such as Extended Spectrum Beta-Lactamase (ESBL) and ampicillinase (AmpC). As a result, carbapenems such as meropenem, imipenem, and ertapenem have been less effective. However, they are still considered when used as part of combination therapy (Tumbarello *et al.*, 2012). Despite all the information noted above antibiotic choices for CRE are still quite restricted, with tigecycline, aminoglycosides, fosfomycin, and polymyxins serving as the pillars of therapy (Sheu *et al.*, 2019). Therefore, my study will ascertain the most effective treatment for CRE infections to reduce the burden on the healthcare system in KZN.

Research Methodology

Study Design

The study design is a quantitative, retrospective cohort study, and the sample size was determined based on the incidence and prevalence of CRE infections in the study population. The data collection methods involved a review of medical records and laboratory reports, and the statistical analysis plan included descriptive and inferential analysis.

Study Setting and Population

This study targeted patients who were suspected to have CRE infections at Inkosi Albert Luthuli Central Hospital (IALCH) in Durban, South Africa. IALCH is a tertiary care hospital known for its specialized services, including the management of complex infections such as CRE. The population of the study was inclusive of all genders and age groups within the CRE infection scope.

Bias Mitigation Efforts

Throughout the investigation, several procedures were put in place to account for potential biases. Firstly, to ensure the inclusion of pertinent cases and reduce selection bias, thorough checks of medical records and laboratory findings were part of the rigorous data-gathering processes. To account for potential confounding variables and determine independent risk factors linked to CRE infections, statistical studies were utilized, encompassing both descriptive and inferential techniques such as logistic regression.

Data Request

Retrospective data on CRE cases at Inkosi Albert Luthuli Central Hospital from January 1, 2021, to December 31, 2021, was initially requested through AARMS on May 5, 2023. The requested data was then approved on July 11, 2023, as shown by the approval letter.

Sampling and Sample Size

A non-random sampling technique was employed for this study. 534 patients both female and male were included in the study.

Brief Overview of Diagnostic Procedure/s as per Laboratory Standard Operating Procedures

The diagnostic procedures as per the laboratory Standard Operating Procedures (SOPs) at Inkosi Albert Luthuli Central Hospital encompassed a comprehensive approach. In line with the mentioned study design, retrospective cohort analysis focusing on CRE infections, the laboratory procedures involved meticulous steps outlined below.

Standard Operating Procedures for Processing of Blood Cultures (MIC1906)

- The procedure involves detecting microorganisms in a patient's blood for diagnostic and prognostic purposes. Blood cultures are crucial for diagnosing and treating sepsis, which is usually common in CRE infections. Criteria for rejection include blood cultures that are received unlabeled and broken culture bottles.
- Positive blood cultures are subcultured onto culture media that are specific to the suspected organism. The list of cultural media is shown in Table 2.

Table 2: List of media and their respective incubation environments (NHLS IALCH SOP: MIC1906)

MEDIA	INCUBATION TIME	O_2	CO_2	ANAEROBIC
Horse blood agar 5% (BA)	18 – 24 HRS		✓	
Chocolate agar (CHOC)	18 – 24 HRS		✓	
MacConkey agar (MAC)	18 – 24 HRS	✓		
Mueller Hinton agar (MHA)	18 – 24 HRS	✓		
10% blood agar	24 – 48 HRS			✓
10% blood agar with amikacin	24 – 48 HRS			✓

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Antimicrobial susceptibility testing was done on positive cultures using the VITEK 2 automated system. This was done to determine the sensitivity of the tested microorganisms to carbapenems.

Standard Operating Procedures for VITEK 2 System (MIC1587)

- The VITEK 2 is an automated instrument, capable of rapid identification and antimicrobial sensitivity testing of microorganisms.
- The identification is done up to the species level of *Enterobacteriaceae*.
- The Gold standard API technology forms the basis of the VITEK 2 systems identification capacity.
- Antibiotic susceptibility results are reported in terms of MICs (minimum inhibitory concentration), which are more clinically and epidemiologically relevant.
- When employing the VITEK 2 automated microbial identification and antimicrobial susceptibility testing system in clinical microbiology laboratories, quality control (QC) is crucial to guaranteeing the precision and dependability of results.
- Daily start-up checks, matching patient samples with QC materials supplied by the manufacturer, and confirming the instrument's operational parameters are all part of the quality control procedure.
- Before standard testing, quality control (QC) is carried out using several grades of QC materials to evaluate performance over a range of concentrations. It is essential to thoroughly document all QC operations, including any deviations and corrective measures.
- In the event of QC failures, troubleshooting is carried out quickly, and routine evaluation of QC data facilitates the discovery of patterns or changes in system performance. The upkeep of high standards in microbiological testing is facilitated by staff training and external quality assurance initiatives. Effective quality control procedures on the VITEK 2 system depend on adherence to the manufacturer's instructions and suggestions.

Statistical Analysis

The data were entered and analyzed using the SPSS statistical software version 16. In all cases, P-values less than 0.05 were considered statistically significant. Initially, the association between each exposure and the presence of infection was assessed using the Mann-Whitney U tests. Cohen's d values were computed to measure the strength of association. To determine independent risk factors for infection, logistic regression analysis was employed.

Ethical Considerations

Permission to proceed with this study was requested from the Mangosuthu University of Technology Research Ethics Committee (MUTREC). Following MUTREC's confirmation of ethical clearance (REF: RD5/04/2023), the study proceeded under the supervision of the assigned supervisor. There was no physical interaction with study participants or patients in this study. As a result, no informed consent was required. When gathering patient information, confidentiality was maintained. Specific details such as hospital episode numbers in the dataset that could potentially identify patients were removed

Research Results/Findings

Descriptive Analysis

The depersonalized data was ethically obtained from Inkosi Albert Luthuli Central Hospital in Durban, South Africa. As is the procedure, data cleaning (the process of finding and fixing inconsistencies in a dataset) was the first step in the analysis. As part of cleaning, the age variable which was noted in years, months, and days- was coded into four age ranges as shown in Figure for simplicity. The raw data had about 24 sub-families of the CRE-causing microorganisms which were aggregated into ten main families shown in Figure 3.

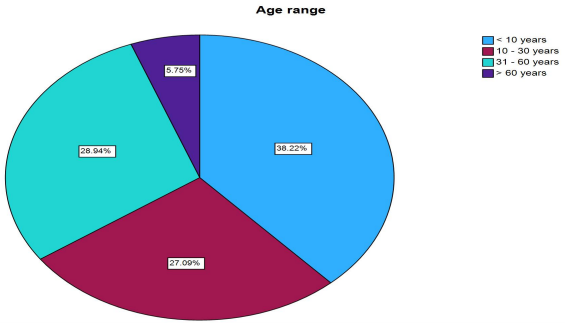

Figure 3: Patient Age for the Recorded Cases

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The majority of the recorded cases were from patients aged less than 10 years. Cases for the age range 10 – 30 years and 31 – 60 years were almost equal, that is 27.09% and 28.94% respectively. Only a few cases were of patients above 60 years of age. The data had 54.92% cases of male patients and 45.08% cases of female patients as shown in Figure 4.

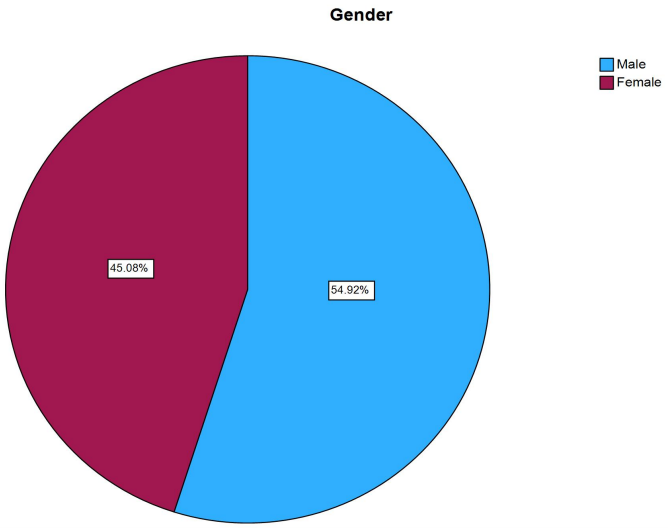

Figure 4: Patient Gender for the Recorded Cases

RQ1: How prevalent are CRE infections in hospitalized patients at Inkosi Albert Luthuli Central Hospital in Durban, South Africa?

As the name suggests, carbapenem-resistant *Enterobacteriaceae* (CRE) are microorganisms that are resistant to carbapenems such as ertapenem, imipenem, and meropenem. To determine their prevalence, the researcher was interested primarily in cases whose laboratory testing results showed that the microorganisms were resistant to at least one of the three carbapenems. Therefore, to achieve this, the frequency of cases was grouped into three groups. These three groups were under the following headings: sensitive, intermediate, and lastly, resistant as shown results in Table 3.

Table 2: CREs Prevalence at Inkosi Albert Luthuli Central Hospital

Antimicrobial Agent	Sensitive	Intermediate	Resistant	Total
Ertapenem	264	20	72	356
Imipenem	338	40	115	493
Meropenem	410	11	113	534

Table 3 shows that of the 356 cases tested with ertapenem, 21.1% were resistant and 5.6% were partially resistant. Of the 493 cases tested with Imipenem, 23.3% were resistant and 8.1% were partially resistant. Meropenem was tested on 534 cases, and 21.2% were found to be resistant, while 2.1% were partially resistant. These results show an average of 21.8% prevalence of CREs and an average of 5.3% partial CREs.

RQ2: Which Enterobacteriaceae are prevalent in CRE infections at Inkosi Albert Luthuli Central Hospital in Durban, South Africa?

Figure 5 presents the descriptive statistics (frequencies) of the different *Enterobacteriaceae*cases recorded at Inkosi Albert Luthuli Central Hospital in Durban, South Africa

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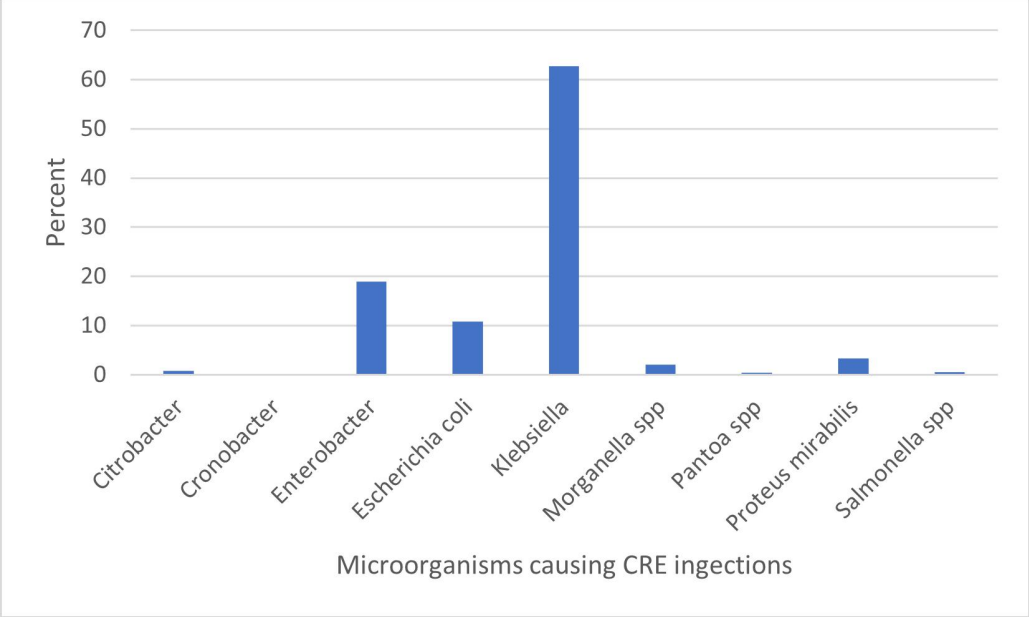

Figure 2: *Enterobacteriaceae* prevalent in CRE infections at Inkosi Albert Luthuli Central Hospital in Durban, South Africa

Figure: *Enterobacteriaceae*prevalent in CRE infections at Inkosi Albert Luthuli Central Hospital in Durban, South Africa

The results show that the most prevalent microorganism groups were the *Klebsiella spp.* (62.7%), followed by *Enterobacter spp.* (18.9%) and *Escherichia coli* (10.8%). On the other hand, the other microorganism families score very low. Further analysis was conducted to determine resistance in terms of carbapenem type. In this case, the carbapenems were ertapenem, imipenem, and meropenem. The results are presented in Tables 4, 5, and 6.

Table 4: CREs due to Microorganism Resistance to Ertapenem

Microorganisms causing CRE	Sensitive	Intermediate	Resistant	Total
Citrobacter spp.	2	0	0	2
Cronobacter spp.	1	0	0	1
Enterobacter spp.	53	1	2	56
Escherichia coli	44	0	0	44
Klebsiella spp.	143	19	70	232
Morganella spp.	7	0	0	7
Pantoea spp.	0	0	0	0
Proteus Mirabilis	12	0	0	12
Salmonella spp.	2	0	0	2
Total	264	20	72	356

Table 5 shows that ertapenem was effective in treating the stated microorganisms, that is 264 (74.2%) of the identified cases, the microorganisms were sensitive to ertapenem, compared to 72 (20.2%) cases that were resistant and 20 (5.6%) that were partially resistant. A further analysis of individual microorganism families indicated that only *Klebsiella spp.* and *Enterobacter spp.* were resistant to ertapenem. Seventy (30.2%) of *Klebsiella* cases were resistant to ertapenem, while 19 (8.2%) were partially resistant. Only two of the *Enterobacter* cases (3.6%) showed resistance to ertapenem and one was partially resistant (1.8%).

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Table 5: CREs due to Microorganism Resistance to Imipenem

Microorganisms causing CRE	Sensitive	Intermediate	Resistant	Total
Citrobacter spp.	3	0	0	3
Cronobacter spp.	1	0	0	1
Enterobacter spp.	80	7	4	91
Escherichia coli	57	0	0	57
Klebsiella spp.	184	22	107	313
Morganella spp.	4	2	2	8
Pantoea spp.	1	0	0	1
Proteus mirabilis	3	9	2	14
Salmonella spp.	3	0	0	3
Total	336	40	115	493

The above results show that 338 (68.6%) cases across the ten microorganism families responded well (sensitive) to imipenem, while 115 (23.3%) were CREs and 40 (8.1%) were partial CREs. At the family level, *Klebsiella spp.* had 107 (34.2%) cases that showed resistance, and 22 (7.02%) showed partial resistance. *Enterobacter* was 4 (4.4%) resistant and 7 (7.7%) partially resistant. *Morganella spp.* and *Proteus mirabilis*, which according to Doi (2019) belong to the Morganellaceae family, had 2 cases each that were resistant to imipenem, and respectively 2 (25%) and 9 (64.3%) that were resistant to imipenem

Table 6: CREs due to Microorganism Resistance to Meropenem

Microorganisms causing CRE	Sensitive	Intermediate	Resistant	Total
Citrobacter spp.	4	0	0	4
Cronobacter spp.	1	0	0	1
Enterobacter spp.	97	2	2	101
Escherichia coli	56	1	0	57
Klebsiella spp.	218	8	111	337
Morganella spp.	11	0	0	11
Pantoea spp.	2	0	0	2
Proteus mirabilis	18	0	0	18
Salmonella spp.	3	0	0	3
Total	410	11	113	534

Similar to the analyses against ertapenem and imipenem, *Klebsiella spp.* had the highest number of cases that showed resistance to Meropenem. Of the 337 cases of *Klebsiella spp.*, 111 (33%) were resistant, 8 (2.4%) were partially resistant, and 218 (64.7%) were sensitive. *Enterobacter spp.* had 2 (0.2%) resistant and 2 (0.2%) partially resistant cases, while *Escherichia coli* had only 1 (1.8%) case that was partially resistant to meropenem.

Inferential Analysis

RQ3: Are there differences in the effectiveness of the antimicrobial agents (Ertapenem, Imipenem, and Meropenem) in treating CRE caused by the most popular microorganisms?

To answer this question, only the three most prevalent microorganisms were considered for hypothesizing, and these were *Klebsiella spp.*, *Enterobacter spp.*, and *Escherichia coli* as shown in Figure 5. For each microorganism, three hypotheses about the effectiveness of the three antimicrobial agents were formulated. Mann-Whitney Test was utilized to test the effectiveness of the three antimicrobial agents in treating *Klebsiella spp.* (*Ha1 - Ha3*),*Enterobacter spp.* (*Hb1 - Hb3*) and *Escherichia coli* (*Hc1 - Hc3*) groups of microorganisms, and the results are presented in the tables below.

Klebsiella Hypotheses

Ha1: There is a significant difference in the effectiveness of ertapenem in treating *Klebsiella spp.* Compared to other carbapenems.

Ha2: There is a significant difference in the effectiveness of imipenem alongside ertapenem in treating *Klebsiella spp.* Compared to meropenem.

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Ha3: There is a significant difference in the effectiveness of meropenem alongside ertapenem in treating *Klebsiella spp.* Compared to imipenem.

Table 7: Effectiveness of antimicrobial agents on Klebsiella spp. (Test Statistics)

	Effectiveness of Ertapenem	Effectiveness of Imipenem	Effectiveness of Meropenem
Mann-Whitney *U*	31179.500	25893.000	23050.500
Wilcoxon W	51480.500	46194.000	43351.500
Z score	-1.794	-5.447	-8.415
P-value	.073	<.001	<.001
Effect size (*d*)		.23	.36

For, the results show that there is no significant difference in the effectiveness of ertapenem between using *Klebsiella spp.* (Median = 1, n = 338) and other antimicrobial agents (Median = 1, n = 201), U = 31179.5, z = -1.794, p = .073. The hypothesis is not supported. On the contrary, the results support *Ha2* (U= 25893, z = -5.447, p < .001) and *Ha3* (U= 23050.5, z = -8.415, p < .001). Furthermore, effect sizes were calculated to determine the extent of the differences for imipenem and meropenem. Using Cohen's (1988) benchmarks for interpreting effect sizes, the results show that the effectiveness difference for imipenem is small (d = .23) and moderate (r = .36) for meropenem.

Enterobacter Hypotheses

Hb1: There is a significant difference in the effectiveness of ertapenem in treating *Enterobacter spp.* Compared to other carbapenems.

Hb2: There is a significant difference in the effectiveness of imipenem and ertapenem in treating *Enterobacter spp.* Compared to meropenem.

Hb3: There is a significant difference in the effectiveness of meropenem alongside ertapenem in treating *Enterobacter spp.* Compared to imipenem.

Table 8: Effectiveness of antimicrobial agents on Enterobacter sp. (Test Statistics)

	Effectiveness of Ertapenem	Effectiveness of Imipenem	Effectiveness of Meropenem
Mann-Whitney *U*	21486.000	18007.000	16902.000
Wilcoxon W	117189.000	23260.000	22155.000
Z score	-.636	-3.564	-5.124
P-value	.525	<.001	<.001
Effect size (*d*)		.15	.22

The results in Table 8 are similar to those of *Ha1 -Ha3* tests in Table 7. *Hb1*is not supported as the results show that there is no significant difference in the effectiveness of Ertapenem between using *Enterobacter* (Median = 2, n= 338) and other antimicrobial agents (Median = 2, n = 201), U = 21486, z = -.636, p = .525. The hypothesis is not supported. On the contrary, the results support *Hb2* (U = 18007, z= -3.564, p < .001) and *Hb3* (U = 16902, z= -5.124, p < .001). Similar to the hypotheses above (*Ha2*and *Ha3*), effect sizes for *Hb2* and *Hb3*were calculated to determine the extent of the difference, and the result shows that the differences are small (d = .15) and Meropenem (d = .22) (Cohen, 1988).

Escherichia coli Hypotheses

Hc1: There is a significant difference in the effectiveness of Ertapenem in treating *Escherichia colic compared* to other antimicrobial agents.

Hc2: There is a significant difference in the effectiveness of Imipenem Ertapenem in treating *Escherichia coli* compared to other antimicrobial agents.

Hc3: There is a significant difference in the effectiveness of Ertapenem *in treating Escherichia coli compared to other antimicrobial agents*.

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Table 9: Effectiveness of antimicrobial agents on *Escherichia coli* (Test Statistics)

	Effectiveness of Ertapenem	Effectiveness of Imipenem	Effectiveness of Meropenem
Mann-Whitney *U*	11225.000	8265.000	10634.000
Wilcoxon W	12936.000	9976.000	12345.000
Z score	-2.734	-5.983	-3.987
P-value	.006	<.001	<.001
Effect size (*d*)	.12	.26	.17

The results in Table 9 support *Hc1* that there is a significant difference in the effectiveness of ertapenem between using *Escherichia coli* (Median = 2, *n* 338) and other carbapenems (Median = 2, *n* = 201), *U* = 21486, *z*= -.636, *p* = .525. Hypotheses *Hc2* (*U* = 21486, *z*= -.636, *p* = .525) and *Hc3* (*U* = 21486, *z*= -.636, *p* = .525) were also supported. The effect sizes were calculated to determine the extent of the differences. Using Cohen's (1988) benchmarks for interpreting effect sizes, the results show that the effectiveness difference for the three antimicrobial agents in treating *Escherichia coli* is all small, with ertapenem (*d*= .12), imipenem (*d* = .26) and meropenem (*d* = .17).

Discussion and Analysis of Results

Demographics

Patient Profile

Findings regarding the frequency of carbapenem-resistant *Enterobacteriaceae* (CRE) infections among hospitalized patients from Inkosi Albert Luthuli Central Hospital in Durban, South Africa, were obtained. Most cases that were reported included patients under the age of ten, suggesting that this age range is particularly vulnerable to CRE infections. One way to discover potential age-related risk factors for CRE infections was to look at the distribution of cases across various age ranges, as shown in Figure 3. A possible gender-related trend that should be investigated in further research was suggested by the data, which also showed a gender distribution with 45.08% of instances in female patients and 54.92% in male patients, as shown in Figure 4.

Clinical Characteristics

The patients included in the research on CRE infections at IALCH most likely displayed a range of clinical traits typical of a setting that provides tertiary care. Most were in immunocompromised states, which made them more vulnerable to infections linked to hospital settings like CRE. Several of them had recently been hospitalized, had undergone invasive treatments including surgery or indwelling catheters, and had previously received antimicrobial medication, especially broad-spectrum antibiotics. Clinical presentations ranged from minor localized infections to severe sepsis or septic shock, and positive cultures from a variety of clinical specimens were frequently required for microbiological confirmation.

Distribution and Significance of Carbapenems

Based on the findings of three different carbapenems which are ertapenem, imipenem, and meropenem, cases were divided into sensitive, intermediate, and resistant groups to determine the prevalence of CRE infections. It was discovered that 21.8% of CREs were present overall (i.e., resistant to any of the three carbapenems), and a further 5.3% displayed partial resistance. Notably, the resistance rates to imipenem (23.3%), meropenem (21.2%), and ertapenem (21.1%) contributed to the total prevalence. These findings emphasize the high prevalence of CRE infections in hospitals and the necessity of efficient management and infection control practices.

Significance of Imipenem Percentage Distribution

A resistance rate of 23.3% was seen for imipenem, a crucial carbapenem in the antimicrobial spectrum, in the CRE cases under investigation. This significant degree of resistance highlights the difficulties in using imipenem, a broad-spectrum antibiotic frequently used in clinical settings, to treat CRE infections. The establishment of imipenem-resistant strains of microorganisms may accelerate the spread of resistance genes among populations of other microorganisms (Tunyong *et al.*, 2021). This is significant because it reduces the number of antibiotics that work in treating infections.

Significance of Meropenem Percentage Distribution

Similarly, meropenem, another potent carbapenem, displayed a resistance rate of 21.2%. As a frontline antibiotic, meropenem's efficacy is compromised by this significant prevalence of resistance. This finding emphasizes the urgency of developing targeted treatment regimens and exploring new antimicrobial options to address CRE infections that exhibit resistance to meropenem.

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Significance of Ertapenem Percentage Distribution

Ertapenem's resistance of 21.1% poses a significant challenge in clinical settings due to its impact on treatment options for CRE infections. Ertapenem, a crucial carbapenem antibiotic, is often employed against multidrug-resistant bacteria. Resistance limits its efficacy, leading to increased morbidity and mortality rates, as indicated by studies such as (Perovic *et al.*, 2020). Beyond clinical implications, ertapenem resistance is associated with heightened healthcare costs, requiring the use of alternative, often more expensive, antibiotics (Delobelle, 2013).

Distribution and Significance of *Enterobacteriaceae* in CRE patients

The diverse and clinically significant family of microorganisms known as Enterobacteriaceae includes a broad range of Gram-negative organisms that are frequently found in a variety of ecological spaces, including the gastrointestinal tracts of humans and other animals. The facultative anaerobic nature of this bacterial family allows it to flourish in both aerobic and anaerobic conditions. Several genera make up the *Enterobacteriaceae family*, each of which contains unique species with potential pathogenicity that can cause a variety of human infections. *Escherichia coli*, *Enterobacter*, *Salmonella*, and *Klebsiella* are a few of this family's well-known members. Some *Enterobacteriaceae* species are important to clinical microbiology and public health because, in addition to their role as typical microbiota inhabitants, they can cause a wide range of infections, from gastrointestinal disorders to systemic infections.

According to a thorough analysis of CRE prevalence, the most common microorganisms were *Klebsiella spp.* (62.7%), *Enterobacter spp.*(18.9%), and *Escherichia coli* (10.8%). This also correlated with the findings of a study that was conducted by Logan and Weinstein (2017). This distribution serves as a basis for focused therapies and is essential for comprehending the landscape of CRE infections. The prevalence rates of other microorganism families were lower, highlighting the dominance of certain *Enterobacteriaceae* in CRE patients.

Significance of Klebsiella Percentage Distribution

The genus *Klebsiella* comprises multiple species of microorganisms that are known to cause various infections in humans. *Klebsiella pneumonia is* one of the most clinically significant species (Duin and Doi, 2017). It is linked to several kinds of infections, including septicemia, urinary tract infection, and pneumonia.

According to the analysis provided, *Klebsiella* is a major contributor to the problem of carbapenem resistance. This is demonstrated by the significance of its 62.7% prevalence in CRE infections. Given the high prevalence, it is likely that *Klebsiella*, particularly the carbapenem-resistant strains, is a major factor in the development of CRE infections. For researchers and clinicians alike, this information is vital because it highlights the need for focused treatment approaches to combat CRE linked to Klebsiella.

Treatment options are drastically reduced when *Klebsiella*develops resistance to carbapenems, which poses a serious risk to public health. The increasing resistance of *Klebsiella* to antibiotics, particularly carbapenems, portends a dire situation in which infections become more difficult to treat, increasing the rates of morbidity and death in those afflicted.

Significance of EnterobacterPercentage Distribution

The genus *Enterobacter* is a member of the *Enterobacteriaceae family* of microorganisms which is also home to well-known microorganisms like *Klebsiella and Escherichia coli*. Both the human gastrointestinal system and the environment frequently contain *Enterobacter* species. Although *Enterobacter usually* causes no harm to healthy people, when it develops antibiotic resistance, it can become a serious threat and cause difficult-to-treat infections. *Enterobacter* was present in 18.9% of CRE patients, suggesting that it significantly contributes to the overall burden of antibiotic resistance. Urinary tract infections, bloodstream infections, respiratory infections, and intra-abdominal infections are just a few of the ways that *Enterobacter* infections can appear. (Breijyeh *et al.*, 2020). The clinical significance of *Enterobacter*'s prevalence among CRE cases is increased by its capacity to cause a variety of infections.

Significance of Escherichia coli Percentage Distribution

The Gram-negative bacterium *Escherichia coli*, also referred to as E. *Coli*, is a typical resident of the human digestive system. Even though the majority of *E. coli* strains are benign and essential to digestion, some pathogenic strains such as can lead to a range of infections. Bloodstream infections, pneumonia, urinary tract infections, and mild gastroenteritis are just a few of the severe infections that *E. coli* can cause (Breijyeh *et al.*, 2020).

Monitoring and addressing resistance patterns is crucial, as evidenced by the relatively high prevalence of *E. coli* among CRE cases (10.8%). Healthcare practitioners must adjust treatment strategies for *E. coli* infections because of the emergence of carbapenem resistance in this

microorganism, which makes infection management more difficult.

Efficacy of Carbapenems

Inferential studies were performed to evaluate the efficacy of carbapenems (ertapenem, imipenem, and meropenem) against the most common microorganisms (*Klebsiella spp.*, *Enterobacter spp.,* and *Escherichia coli*). The results showed that there was no significant difference between ertapenem and other carbapenems in terms of their efficacy against *Klebsiella spp*. Meropenem, on the other hand, demonstrated the maximum effectiveness, whereas imipenem and meropenem exhibited notable variances. These results imply that meropenem might be a better choice for treating infections caused by *Klebsiella spp*. In addition to the aforementioned, the same findings of this study were also discovered in a study conducted by Tumbarello *et al.* (2022). In their study, they aimed to determine the effectiveness of meropenem for infections caused by KPC-producing *Klebsiella pneumoniae*.

In the case of *Enterobacter spp.*, there was no significant difference in the effectiveness of ertapenem compared to the other two carbapenems. However, both imipenem and meropenem exhibited significant differences, with meropenem again being more effective. These results echo the *Klebsiella spp.* Findings emphasize the potential efficacy of meropenem against a broader spectrum of microorganisms.

All three carbapenems demonstrated notable variations in their efficacy against *Escherichia coli*, with imipenem demonstrating the highest level of effectiveness, trailed by meropenem and ertapenem. Although statistically significant, the practical importance of these differences may be restricted, as indicated by the relatively small effect sizes.

The need for focused treatments and the creation of efficient treatment regimens is highlighted by the high frequency of CRE infections, particularly among microorganisms. While imipenem showed greater efficacy against *Escherichia coli*, the results point to the possible advantage of meropenem in treating infections caused by *Klebsiella spp.* and *Enterobacter spp*. (Tumbarello *et al.*, 2022). These understandings help direct antimicrobial stewardship initiatives and clinical decision-making to maximize treatment outcomes.

In summary, the aforementioned findings, which looked at the variations in the antimicrobial drugs' (Ertapenem, Imipenem, and Meropenem) efficacy in treating CRE brought on by the most common microorganisms (i.e. *Klebsiella spp.*, *Enterobacter spp.*, and *Escherichia coli*) address the study's purpose. This is accomplished by providing the Mann-Whitney Test results, which demonstrate the statistical significance and effect sizes of the variations in antimicrobial effectiveness, for each hypothesis about these bacteria.

Generalizability

The study's findings can be generalized to a larger population by using random or stratified sampling techniques. The Mann-Whitney Test indicates significant differences in antimicrobial agent effectiveness, indicating the findings are not random chance and applicable to a larger population.

Another crucial component is the use of confidence intervals, which offer a range that the actual population parameters should fall inside. This aids in comprehending the accuracy and dependability of the study's conclusions when extrapolated to a bigger group. Furthermore, reporting effect sizes is necessary to understand how much antibiotic effectiveness varies. Greater effect sizes suggest that the results will probably be useful to a wider range of people.

To validate the results, it is strongly advised that the study be repeated in various populations and circumstances. The likelihood of extrapolating the findings is increased when comparable outcomes are observed in several investigations. When extrapolating the results, contextual variables including patient demographics, healthcare settings, and geographic location should be considered. Ensuring the similarity of these factors in the larger population facilitates the creation of more precise generalizations.

Lastly, it is critical to offer mechanistic insights into the observed variations in antibiotic effectiveness. Applying these results to other groups may be made easier by comprehending the reasons why some antimicrobials work better than others. By addressing these issues, it will be easier to extrapolate the study results on the efficacy of ertapenem, imipenem, and meropenem in treating CRE to broader populations, which will support the creation of treatment guidelines and policies in various healthcare settings.

Conclusion

In addition to highlighting the necessity of continuing surveillance and study in the field of antibiotic resistance, the thorough examination of patient demographics, CRE prevalence, and microorganisms' distribution lays the groundwork for focused interventions. The results offer significant perspectives on the worldwide endeavor to counteract CRE infections and encourage the responsible use of antibiotics.

Klebsiella spp. were found to be the most common microorganisms, followed by *Enterobacter spp.* and *Escherichia coli*. Antimicrobial drugs were evaluated for their effectiveness against common microorganisms. The

results consistently showed that meropenem was more efficient against these microorganisms, particularly against *Klebsiella spp.* and *Enterobacter spp*. Notable efficacy was also demonstrated by imipenem, especially against Escherichia *coli*.

Study Limitations

This study had several limitations that should be considered. First, there were delays in the data request approval process, which affected the timely capture of pertinent data. Furthermore, a major drawback was the lack of patient post-treatment data, which limited the capacity to evaluate the effectiveness and long-term results of therapies. Additionally, because the data was retrospective and depended on previous knowledge, there is a chance that it was skewed or incomplete. These restrictions highlighted the necessity to interpret these findings with caution and point out areas that future research projects should focus on strengthening.

Recommendations

Antimicrobial Stewardship

- Optimize Antimicrobial Use: Encourage the cautious application of carbapenems, emphasizing the preferential use of imipenem and meropenem by the susceptibility of microorganisms.
- Education and Training: Provide healthcare personnel with frequent training sessions on antimicrobial therapy, with a focus on the significance of good prescribing procedures.

Further Research and Collaboration

- Comprehensive Resistance Surveillance: Increase the scope of the study by incorporating thorough resistance surveillance and accounting for other factors such as comorbidities, past antibiotic use, and genetic analysis of resistant organisms.

Collaboration and Data Sharing

To address the local and international problems of CRE infections, promote cooperation amongst healthcare facilities through data exchange and cooperative research projects.

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Conflict of Interest

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References

1) Aboufaycal, H., Sader, H.S., Rolston, K., Deshpande, L.M., Toleman, M., Bodey, G., Raad, I. and Jones, R.N., 2007. bla VIM-2 and bla VIM-7 carbapenemase-producing Pseudomonas aeruginosa isolates detected in a tertiary care medical center in the United States: report from the MYSTIC program. Journal of Clinical Microbiology, 45(2), pp.614-615.
2) Akullian, A., Vandormael, A., Miller, J.C., Bershteyn, A., Wenger, E., Cuadros, D., Gareta, D., Bärnighausen, T., Herbst, K. and Tanser, F., 2021. Large age shifts in HIV-1 incidence patterns in KwaZulu-Natal, South Africa. Proceedings of the National Academy of Sciences, 118(28), p.e2013164118.
3) Andriatahina, T., Randrianirina, F., Hariniana, E.R., Talarmin, A., Raobijaona, H., Buisson, Y. and Richard, V., 2010. High prevalence of fecal carriage of extended-spectrum β-lactamase-producing *Escherichia coli* and *Klebsiella pneumonia* in a pediatric unit in Madagascar. BMC Infectious Diseases, 10(1), pp.1-8.
4) Bamford, L.J., McKerrow, N.H., Barron, P. and Aung, Y., 2018. Child mortality in South Africa: Fewer deaths, but better data are needed. South African Medical Journal, 108(3), pp.25-32.

5) Barguigua, A., Zerouali, K., Katfy, K., El Otmani, F., Timinouni, M. and Elmdaghri, N., 2015. Occurrence of OXA-48 and NDM-1 carbapenemase-producing *Klebsiella*pneumoniae in a Moroccan university hospital in Casablanca, Morocco. Infection, Genetics and Evolution, 31, pp.142-148.
6) Breijyeh, Z., Jubeh, B. and Karaman, R., 2020. Resistance of gram-negative bacteria to current antibacterial agents and approaches to resolve it. Molecules, 25(6), p.1340.
7) Brink, A., Coetzee, J., Clay, C., Corcoran, C., Van Greune, J., Deetlefs, J.D., Nutt, L., Feldman, C., Richards, G., Nordmann, P. and Poirel, L., 2012. The spread of carbapenem-resistant *Enterobacteriaceae* in South Africa: risk factors for acquisition and prevention: forum-issue in medicine. South African Medical Journal, 102(7), pp.599-601.
8) Cantón, R., Akóva, M., Carmeli, Y., Giske, C.G., Glupczynski, Y., Gniadkowski, M., Livermore, D.M., Miriagou, V., Naas, T., Rossolini, G.M. and Samuelsen, Ø., 2012. Rapid evolution and spread of carbapenemases among *Enterobacteriaceae in* Europe. Clinical microbiology and infection, 18(5), pp.413-431.
9) Centers for Disease Control and Prevention. 2019. Antibiotic Resistance Threats in the United States. Atlanta, GA: U.S. Department of Health and Human Services, 23 November 2021 [Online]. Available at: www.cdc.gov/DrugResistance/Biggest-Threats.html. DOI: http://dx.doi.org/10.15620/cdc:82532. [Accessed 21 September 2022]
10) Codjoe, F.S. and Donkor, E.S., 2017. Carbapenem resistance: a review. Medical Sciences, 6(1), p.1.
11) Cuzon, G., Bentchouala, C., Vogel, A., Héry, M., Lezzar, A., Smati, F., Dortet, L. and Naas, T., 2015. The first outbreak of OXA-48-positive carbapenem-resistant *Klebsiella pneumonia* isolates in Constantine, Algeria. International journal of antimicrobial agents, 46(6), pp.725-727.
12) Delobelle, P., 2013. The health system in South Africa. Historical perspectives and current challenges. South Africa in focus: Economic, political, and social issues. New York, NY: Nova Science Publishers, Inc, pp.159-205.
13) Demir, S., Soysal, A., Bakir, M., Kaufmann, M.E. and Yagci, A., 2008. Extended-spectrum β-lactamase-producing*Klebsiella* pneumonia in pediatric wards: A nested case-control study. Journal of Paediatrics and Child Health, 44(10), pp.548-553.
14) Egan, A.J., Cleverley, R.M., Peters, K., Lewis, R.J. and Vollmer, W., 2017. Regulation of bacterial cell wall growth. *The FEBS journal*, *284*(6), pp.851-867.
15) Goodman, K.E., Simner, P.J., Tamma, P.D. and Milstone, A.M., 2016. Infection control implications of heterogeneous resistance mechanisms in carbapenem-resistant *Enterobacteriaceae*(CRE). Expert review of anti-infective therapy, 14(1), pp.95-108.
16) Govind, C.N., Moodley, K., Peer, A.K., Pillay, N., Maske, C., Wallis, C., Viana, R., Chetty, A. and Perovic, O., 2013. NDM-1 imported from India–first reported case in South Africa. South African Medical Journal, 103(7), pp.476-478.
17) Guh, A.Y., Bulens, S.N., Mu, Y., Jacob, J.T., Reno, J., Scott, J., Wilson, L.E., Vaeth, E., Lynfield, R., Shaw, K.M. and Vagnone, P.M.S., 2015. Epidemiology of carbapenem-resistant *Enterobacteriaceae* in 7 US communities, 2012-2013. Jama, 314(14), pp.1479-1487.
18) Gulumbe, B.H. and Ajibola, O., 2020. Carbapenem Resistant *Enterobacteriaceae* in Africa. *Borneo Journal of Pharmacy*, *3*(2), pp.71-78.
19) Hammami, S., Gautier, V., Ghozzi, R., Da Costa, A., Ben-Redjeb, S. and Arlet, G., 2010. Diversity in VIM-2-encoding class 1 integrons and occasional blaSHV2a carriage in isolates of a persistent, multidrug-resistant Pseudomonas aeruginosa clone from Tunis. Clinical Microbiology and Infection, 16(2), pp.189-193.
20) Hasan, C.M., Dutta, D., and Nguyen, A.N., 2021. Revisiting antibiotic resistance: mechanistic foundations to evolutionary outlook. *Antibiotics*, *11*(1), p.40.
21) Hlongwa, M. and De Wet, N., 2019. Demographic and socioeconomic factors associated with under-5 mortality in KwaZulu-Natal, South Africa. South African Journal of Child Health, 13(4), pp.174-179.
22) Hsu, L.Y., Apisarnthanarak, A., Khan, E., Suwantarat, N., Ghafur, A. and Tambyah, P.A., 2017. Carbapenem-resistant Acinetobacter baumannii and *Enterobacteriaceae* in south and south east Asia. Clinical microbiology reviews, 30(1), pp.1-22.
23) Jacobson, R.K., Minenza, N., Nicol, M. and Bamford, C., 2012. VIM-2 metallo-β-lactamase-producing Pseudomonas aeruginosa causing an outbreak in South Africa. Journal of

Antimicrobial Chemotherapy, 67(7), pp.1797-1798.

24) Kharsany, A.B., McKinnon, L.R., Lewis, L., Cawood, C., Khanyile, D., Maseko, D.V., Goodman, T.C., Beckett, S., Govender, K., George, G., and Ayalew, K.A., 2020. Population prevalence of sexually transmitted infections in a high HIV burden district in KwaZulu-Natal, South Africa: Implications for HIV epidemic control. International Journal of Infectious Diseases, 98, pp.130-137.
25) Kheyrodin, H., Jami, R., and Rehman, F.U., 2022. Cellular structure and molecular functions of plants, animals, microorganisms, and viruses. *Cellular, Molecular and Biomedical Reports*, *2*(1), pp.33-41.
26) Kohanski, M.A., Dwyer, D.J. and Collins, J.J., 2010. How antibiotics kill microorganisms: from targets to networks. Nature Reviews Microbiology, 8(6), pp.423-435.
27) Krishinchand, H., Naidoo, K., Mahabeer, P., and Archery, M., 2021. Pediatric *Enterobacteriaceae infections* in hospitalized children in Durban, KwaZulu-Natal. Southern African Journal of Infectious Diseases, 36(1), p.6.
28) Kumarasamy, K.K., Toleman, M.A., Walsh, T.R., Bagaria, J., Butt, F., Balakrishnan, R., Chaudhary, U., Doumith, M., Giske, C.G., Irfan, S. and Krishnan, P., 2010. The emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study. *The Lancet Infectious Diseases*, *10*(9), pp.597-602.
29) Lafeuille, E., Decré, D., Mahjoub-Messai, F., Bidet, P., Arlet, G. and Bingen, E., 2013. OXA-48 carbapenemase-producing *Klebsiella* pneumoniae isolated from Libyan patients. Microbial drug resistance, 19(6), pp.491-497.
30) Lee, B.Y., Bartsch, S.M., Wong, K.F., Kim, D.S., Cao, C., Mueller, L.E., Gussin, G.M., McKinnell, J.A., Miller, L.G. and Huang, S.S., 2019. Tracking the spread of carbapenem-resistant *Enterobacteriaceae* (CRE) through clinical cultures alone underestimates the spread of CRE even more than anticipated. Infection Control & Hospital Epidemiology, 40(6), pp.731-734.
31) Li, Y., Sun, Q.L., Shen, Y., Zhang, Y., Yang, J.W., Shu, L.B., Zhou, H.W., Wang, Y., Wang, B., Zhang, R. and Wang, S., 2018. The rapid increase in the prevalence of carbapenem-resistant *Enterobacteriaceae* (CRE) and the emergence of colistin resistance gene mcr-1 in CRE in a hospital in Henan, China. Journal of Clinical Microbiology, 56(4), pp.e01932-17.
32) Livermore, D.M., 2012. Fourteen years in resistance. *International journal of antimicrobial agents*, *39*(4), pp.283-294.
33) Logan, L.K. and Weinstein, R.A., 2017. The epidemiology of carbapenem-resistant *Enterobacteriaceae*: the impact and evolution of a global menace. The Journal of infectious diseases, 215(suppl_1), pp.S28-S36.
34) Lolans, K., Queenan, A.M., Bush, K., Sahud, A. and Quinn, J.P., 2005. First nosocomial outbreak of Pseudomonas aeruginosa producing an integron-borne metallo-β-lactamase (VIM-2) in the United States. Antimicrobial agents and chemotherapy, 49(8), pp.3538-3540.
35) Lyman, M., Walters, M., Lonsway, D., Rasheed, K., Limbago, B. and Kallen, A., 2015. Notes from the field: carbapenem-resistant *Enterobacteriaceae* producing OXA-48-like carbapenemases—United States, 2010–2015. MMWR Morb Mortal Wkly Rep, 64(47), pp.1315-1316.
36) Madni, O., Amoako, D.G., Abia, A.L.K., Rout, J. and Essack, S.Y., 2021. Genomic Investigation of Carbapenem-Resistant *Klebsiella* Pneumonia Colonization in an Intensive Care Unit in South Africa. Genes, 12(7), p.951.
37) Marchionne, M.D., Torres, L.M., Hartley, D.M., Koch, M., and Goodman, J.L., 2019. Carbapenem and colistin resistance in *Enterobacteriaceae* in Southeast Asia: review and mapping of emerging and overlapping challenges. *International journal of antimicrobial agents*, *54*(4), pp.381-399.
38) Maltezou, H.C., Giakkoupi, P., Maragos, A., Bolikas, M., Raftopoulos, V., Papahatzaki, H., Vrouhos, G., Liakou, V. and Vatopoulos, A.C., 2009. The outbreak of infections due to KPC-2-producing *Klebsiella* pneumonia in a hospital in Crete (Greece). Journal of Infection, 58(3), pp.213-219.
39) Manenzhe, R.I., Zar, H.J., Nicol, M.P. and Kaba, M., 2015. The spread of carbapenemase-producing microorganisms in Africa: a systematic review. Journal of antimicrobial chemotherapy, 70(1), pp.23-40.
40) Mezzatesta, M.L., Gona, F., Caio, C., Petrolito, V., Sciortino, D., Sciacca, A., Santangelo, C. and Stefani, S., 2011. The outbreak of KPC-3-producing, and colistin-resistant, *Klebsiella pneumonia* infections in two Sicilian hospitals. Clinical microbiology and infection, 17(9), pp.1444-1447.
41) Miller, S., and Humphries, R.M., 2016. Clinical laboratory detection of carbapenem-resistant and carbapenemase-producing *Enterobacteriaceae*.

Expert review of anti-infective therapy, 14(8), pp.705-717.

42) Mitgang, E.A., Hartley, D.M., Malchione, M.D., Koch, M., and Goodman, J.L., 2018. Review and mapping of carbapenem-resistant *Enterobacteriaceae* in Africa: using diverse data to inform surveillance gaps. International journal of antimicrobial agents, 52(3), pp.372-384.
43) Montagnani, C., Prato, M., Scolfaro, C., Colombo, S., Esposito, S., Tagliabue, C., Lo Vecchio, A., Bruzzese, E., Loy, A., Cursi, L. and Vuerich, M., 2016. Carbapenem-resistant *Enterobacteriaceae* infections in children. The Pediatric Infectious Disease Journal, 35(8), pp.862-868.
44) Munoz-Price, L.S., Poirel, L., Bonomo, R.A., Schwaber, M.J., Daikos, G.L., Cormican, M., Cornaglia, G., Garau, J., Gniadkowski, M., Hayden, M.K. and Kumarasamy, K., 2013. Clinical epidemiology of the global expansion of *Klebsiella pneumonia* carbapenemases. The Lancet Infectious Diseases, 13(9), pp.785-796.
45) Narsai, P., Taylor, M., Jinabhai, C. and Stevens, F., 2013. Variations in housing satisfaction and health status in four lower socio-economic housing typologies in the eThekwini Municipality in KwaZulu-Natal. *Development Southern Africa*, *30*(3), pp.367-385.
46) National Institute for Communicable Diseases. 2022. Carbapenemase-producing *Enterobacteriaceae*(CPE), 17 September 2022. [Online]. Available at: https://www.nicd.ac.za/diseases-a-z-index/carbapenemase-producing-*Enterobacteriaceae*-cpe/ [Accessed 20 September 2022]
47) Nordmann, P., Poirel, L., Toleman, M.A. and Walsh, T.R., 2011. Does broad-spectrum β-lactam resistance due to NDM-1 herald the end of the antibiotic era for the treatment of infections caused by Gram-negative microorganisms? Journal of antimicrobial chemotherapy, 66(4), pp.689-692.
48) Olayiwola, J.O., Ojo, D.A., Balogun, S.A. and Ojo, O.E., 2021. Global Spread of Carbapenem-Resistant Enterobacteriaceae: A Challenging Threat to the Treatment of Bacterial Diseases in Clinical Practice.
49) Osano, E., Arakawa, Y., Wacharotayankun, R., Ohta, M., Horii, T., Ito, H., Yoshimura, F. and Kato, N., 1994. Molecular characterization of an *Enterobacterial*metallo beta-lactamase found in a clinical isolate of Serratia marcescens that shows imipenem resistance. Antimicrobial agents and chemotherapy, 38(1), pp.71-78.
50) Osei Sekyere, J., 2016. The current state of resistance to antibiotics of last resort in South Africa: a review from a public health perspective. Frontiers in public health, 4, p.209.
51) Perovic, O., Ismail, H., Quan, V., Bamford, C., Nana, T., Chibabhai, V., Bhola, P., Ramjathan, P., Swe Swe-Han, K., Wadula, J. and Whitelaw, A., 2020. Carbapenem-resistant *Enterobacteriaceae* in patients with bacteremia at tertiary hospitals in South Africa, 2015 to 2018. European Journal of Clinical Microbiology & Infectious Diseases, 39(7), pp.1287-1294.
52) Pitout, J.D., 2010. The latest threat in the war on antimicrobial resistance. The Lancet Infectious Diseases, 10(9), pp.578-579.
53) Poirel, L., Abdelaziz, M.O., Bernabeu, S. and Nordmann, P., 2013. Occurrence of OXA-48 and VIM-1 carbapenemase-producing *Enterobacteriaceae* in Egypt. International journal of antimicrobial agents, 41(1), pp.90-91.
54) Poirel, L., Potron, A. and Nordmann, P., 2012. OXA-48-like carbapenemases: the phantom menace. Journal of Antimicrobial Chemotherapy, 67(7), pp.1597-1606.
55) Puttaswamy, S., Gupta, S.K., Regunath, H., Smith, L.P. and Sengupta, S., 2018. A comprehensive review of the present and future antibiotic susceptibility testing (AST) systems. Arch Clin Microbiol, 9(3).
56) Queenan, A.M. and Bush, K., 2007. Carbapenemases: the versatile β-lactamases. Clinical microbiology reviews, 20(3), pp.440-458.
57) Sheu, C.C., Chang, Y.T., Lin, S.Y., Chen, Y.H. and Hsueh, P.R., 2019. Infections caused by carbapenem-resistant *Enterobacteriaceae*: an update on therapeutic options. Frontiers in microbiology, 10, p.80.
58) Tamma, P.D. and Simner, P.J., 2018. Phenotypic detection of carbapenemase-producing organisms from clinical isolates. Journal of Clinical Microbiology, 56(11), pp.e01140-18.
59) Temkin, E., Adler, A., Lerner, A. and Carmeli, Y., 2014. Carbapenem-resistant Enterobacteriaceae: biology, epidemiology, and management. Annals of the New York Academy of Sciences, 1323(1), pp.22-42.
60) Thomas, T.S. and Duse, A.G., 2018. Epidemiology of carbapenem-resistant *Enterobacteriaceae*(CRE) and comparison of the phenotypic versus genotypic screening tests for the detection of carbapenemases at a tertiary level, academic hospital in Johannesburg, South Africa. Southern African Journal of Infectious Diseases, pp.1-7.

61) Tompkins, K., Juliano, J.J. and Van Duin, D., 2021. Antimicrobial resistance in *Enterobacter*ales and its contribution to sepsis in Sub-saharan Africa. *Frontiers in medicine*, *8*, p.615649.
62) Touati, M., Diene, S.M., Dekhil, M., Djahoudi, A., Racherache, A. and Rolain, J.M., 2013. Dissemination of a class I integron carrying VIM-2 carbapenemase in Pseudomonas aeruginosa clinical isolates from a hospital intensive care unit in Annaba, Algeria. Antimicrobial agents and chemotherapy, 57(5), pp.2426-2427.
63) Tumbarello, M., Viale, P., Viscoli, C., Trecarichi, E.M., Tumietto, F., Marchese, A., Spanu, T., Ambretti, S., Ginocchio, F., Cristini, F. and Losito, A.R., 2012. Predictors of mortality in bloodstream infections caused by *Klebsiella pneumonia* carbapenemase-producing K. pneumoniae: the importance of combination therapy. Clinical infectious diseases, 55(7), pp.943-950.
64) Tunyong, W., Arsheewa, W., Santajit, S., Kong-Ngoen, T., Pumirat, P., Sookrung, N., Chaicumpa, W. and Indrawattana, N., 2021. Antibiotic resistance genes among carbapenem-resistant Enterobacterales (CRE) isolates of Prapokklao Hospital, Chanthaburi Province, Thailand. Infection and Drug Resistance, pp.3485-3494.
65) Tzouvelekis, L.S., Markogiannakis, A., Psichogiou, M., Tassios, P.T. and Daikos, G.L., 2012. Carbapenemases in *Klebsiella* pneumoniae and other *Enterobacteriaceae*: an evolving crisis of global dimensions. Clinical microbiology reviews, 25(4), pp.682-707.
66) Van Duin, D. and Doi, Y., 2017. The global epidemiology of carbapenemase-producing *Enterobacteriaceae*. Virulence, 8(4), pp.460-469.
67) Vardakas, K.Z., Matthaiou, D.K., Falagas, M.E., Antypa, E., Koteli, A. and Antoniadou, E., 2015. Characteristics, risk factors and outcomes of carbapenem-resistant *Klebsiella pneumonia* infections in the intensive care unit. Journal of Infection, 70(6), pp.592-599.
68) Villegas, M.V., Pallares, C.J., Escandón-Vargas, K., Hernández-Gómez, C., Correa, A., Álvarez, C., Rosso, F., Matta, L., Luna, C., Zurita, J. and Mejía-Villatoro, C., 2016. Characterization and clinical impact of bloodstream infection caused by carbapenemase-producing *Enterobacteriaceae* in seven Latin American countries. PloS one, 11(4), p.e01540
69) Woo, K.S., 2019. Carbapenem-Resistant *Enterobacteriaceae*: Rapid Laboratory Diagnosis and Surveillance Culture for Infection Control. The Korean Journal of Medicine, 94(2), pp.170-172.

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