The bacterial resistance phenomenon in the COVID-19 pandemic scenario in Brazil

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Abstract:
In 2019, the emergence of SARS-CoV-2 caused the global COVID-19 pandemic, leading to high mortality rates due to damage to the respiratory tract and co-infections with multidrug-resistant (MDR) bacteria. In Brazil, more than 37 million cases and 700,000 deaths were recorded due to the association between COVID-19 and resistant bacterial infections. It is estimated that antibiotic-resistant microorganisms cause 1.27 million deaths annually, and these numbers are expected to grow in the coming years due to therapeutic failure with currently available antibiotics. Moreover, the COVID-19 pandemic has affected the prevalence of multidrug-resistant microorganisms. Objective: To report the impact caused by the COVID-19 pandemic associated with the spread of MDR bacteria in hospitalized patients in Brazil. Methodology: The present study is an integrative review on the phenomenon of bacterial resistance in the pandemic scenario of COVID-19 in Brazil. Results and Discussion: Antibiotic resistance is driven by the misuse and unnecessary use of these drugs, as well as by the lack of adequate infection prevention and control. Conclusion: This study confirms the advancement of bacterial resistance in the context of the COVID-19 pandemic, influenced by the length of hospital stays and the reduction of the therapeutic arsenal, contributing to the spread of bacterial infections in human populations.
Keywords: Multidrug resistance, nosocomial infections, antimicrobial resistance, COVID-19, pandemic.

O impacto da Pandemia de COVID-19 no cenário da resistência bacteriana no continente Americano

Resumo:
Em 2019, o surgimento do SARS-CoV-2 causou a pandemia global da COVID-19 promovendo altas taxas de mortalidade pelos danos causados no trato respiratório e as co-infecções com bactérias multidroga-

resistentes (MDR). No Brasil, mais de 37 milhões de casos e 700 mil óbitos foram registrados devido a associação da COVID-19 e as infecções bacterianas resistentes. Estima-se que microrganismos resistentes a antibióticos causem 1,27 milhão de mortes anualmente, e estes números tendem a crescer ao longo dos anos devido a falha terapêutica com os antibióticos existentes atualmente. Além disso, deve-se considerar que a pandemia de COVID-19 afetou a prevalência de microrganismos multirresistentes. **Objetivo:** relatar o impacto causado pela pandemia da COVID-19 associado à disseminação de bactérias MDR em pacientes hospitalizados no Brasil. **Metodologia:** o presente estudo é uma revisão integrativa sobre o fenômeno da resistência bacteriana no cenário pandêmico da COVID-19 no Brasil. **Resultados e Discussão:** a resistência aos antibióticos é impulsionada pelo abuso e uso desnecessário desses medicamentos, assim como pela falta de prevenção e controle adequados de infecções. **Conclusão:** este estudo comprova o avanço da resistência bacteriana frente ao cenário pandêmico da COVID-19 influenciado pelo tempo de internação e a redução do arsenal terapêutico contribuindo para a disseminação das infecções bacterianas em populações humanas.
Palavras-chave: multidroga-resistentes, infecções nosocomiais, resistência antimicrobiana, COVID-19, pandemia.

El impacto de la pandemia de COVID-19 en el panorama de la resistencia bacteriana en el continente americano

Resumen:
En 2019, la aparición del SARS-CoV-2 causó la pandemia global de COVID-19, promoviendo altas tasas de mortalidad debido a los daños causados en el tracto respiratorio y a las co-infecciones con bacterias multirresistentes (MDR). En Brasil, se registraron más de 37 millones de casos y 700 mil muertes debido a la asociación de COVID-19 con infecciones bacterianas resistentes. Se estima que los microorganismos resistentes a antibióticos causan 1,27 millones de muertes anualmente, y estos números tienden a aumentar con el tiempo debido a la falla terapéutica de los antibióticos actualmente disponibles. Además, se debe considerar que la pandemia de COVID-19 ha afectado la prevalencia de microorganismos multirresistentes. **Objetivo:** Reportar el impacto causado por la pandemia de COVID-19 en la diseminación de bacterias MDR en pacientes hospitalizados en Brasil. Metodología: El presente estudio es una revisión integrativa sobre el fenómeno de la resistencia bacteriana en el contexto pandémico de COVID-19 en Brasil. **Resultados y Discusión:** La resistencia a los antibióticos es impulsada por el abuso y el uso innecesario de estos medicamentos, así como por la falta de prevención y control adecuados de las infecciones. **Conclusión:** Este estudio demuestra el avance de la resistencia bacteriana en el contexto pandémico de COVID-19, influenciado por el tiempo de hospitalización y la reducción del arsenal terapéutico, contribuyendo a la diseminación de infecciones bacterianas en las poblaciones humanas.
Palabras clave: multirresistente, infecciones nosocomiales, resistencia a los antimicrobianos, COVID-19, pandemia.

INTRODUCTION

Since December 2019, the world has faced a challenging public health problem due to the global dissemination of SARS-CoV-2. The extent of infection caused by SARS-CoV-2 can vary between asymptomatic patients and patients with mild clinical manifestations and between moderate, severe and critical cases. Currently, according to the World Health Organization (WHO), more than 700 million confirmed cases of COVID-19 and more than 6 million deaths are diagnosed worldwide (Almeida *et al.*, 2023).

The exponential increase in the number of confirmed cases directly reflects coronavirus transmission, which can occur through personal contact through the inhalation of droplets or particles from contaminated secretions, such as saliva droplets, sneezing, or coughing; or through contact with contaminated objects and surfaces, such as touching or holding hands, followed by contact with the mouth, nose or eyes (Jiang *et al*., 2020). After infection, individuals can remain asymptomatic or develop symptoms that can manifest between 2 and 14 days after exposure to the virus and include fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body pain, headaches, taste and smell loss, sore throat, runny nose and nasal congestion, nausea and diarrhea (Jiang *et al.,* 2020).

During the pandemic, in addition to SARS-CoV-2 infection, hospitalized patients presented secondary bacterial infections, especially infections caused by opportunistic microorganisms, which were related to a decrease in survival. Furthermore, the frequency of multidrug-resistant (MDR) bacteria in these patients represents a meaningful public health problem, and new resistance mechanisms are emerging and spreading around the world, threatening the ability to treat common infectious diseases, which can result in prolonged illness, inability and death. Antimicrobial resistance (AMR) increases healthcare costs due to prolonged hospital stays and increased demand for intensive care. The lack of effective antimicrobial agents for preventing and treating infections can affect medical procedure performance, such as organ transplantation, chemotherapy, diabetes control and large surgeries (Lentz, 2022).

Considering the mortality associated with COVID-19 and the health damage inherent to bacterial resistance related to the indiscriminate use of antimicrobial agents, this study is relevant because it provides essential data about the influence of COVID-19 on bacterial resistance rates globally. Therefore, the present study aimed to perform a integrative review of the literature on the impact of the COVID-19 pandemic on the dissemination of MDR bacteria in hospitalized patients in Brazil.

METHODOLOGY

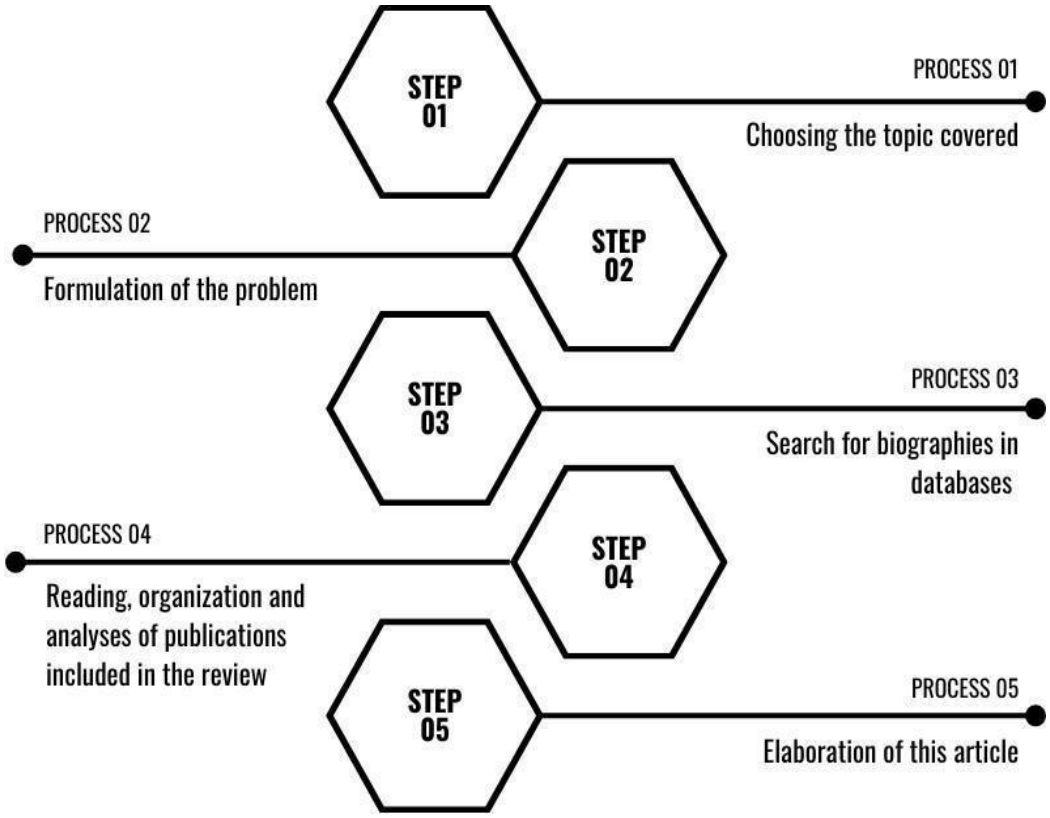
The present study is an integrative review of the phenomenon of bacterial resistance in the COVID-19 pandemic scenario in Brazil. The guiding question that directed this research was formulated with the objective of investigating the influence of the COVID-19 pandemic on bacterial resistance rates. The question posed was: "Is there a higher prevalence of hospitalizations and the incorrect use of antibiotics for COVID-19 related to worsening cases of bacterial infections?" This study aims to clarify the crucial points for the epidemiological understanding of these pathologies.

In this study, articles indexed in the following databases were used: Virtual Health Library (BVS), National Library of Medicine (PubMed), and Google Scholar. For the article search, two controlled vocabularies were employed: DECS (Health Sciences Descriptors) and MeSH (Medical Subject Headings). The selected descriptors were “bacterial drug resistance,” “SARS-CoV-2,” and “antibacterials,” searched separately and in combinations.

After the initial search, the articles were analyzed in two stages. In the first, a screening of the titles and abstracts was carried out, considering the inclusion and exclusion criteria. Then, in the second stage, the selected articles were read in full, applying the inclusion and exclusion criteria again to ensure the relevance of the studies. The inclusion criteria were: original articles published between 2020 and 2023, in English, Spanish, or Portuguese, available in full. The exclusion criteria were: works published in formats other than articles, such as theses and dissertations, incomplete articles, and articles published in languages other than those previously mentioned.

The study began in 2022 and was carried out in five sequential stages in its construction (Figure 1).

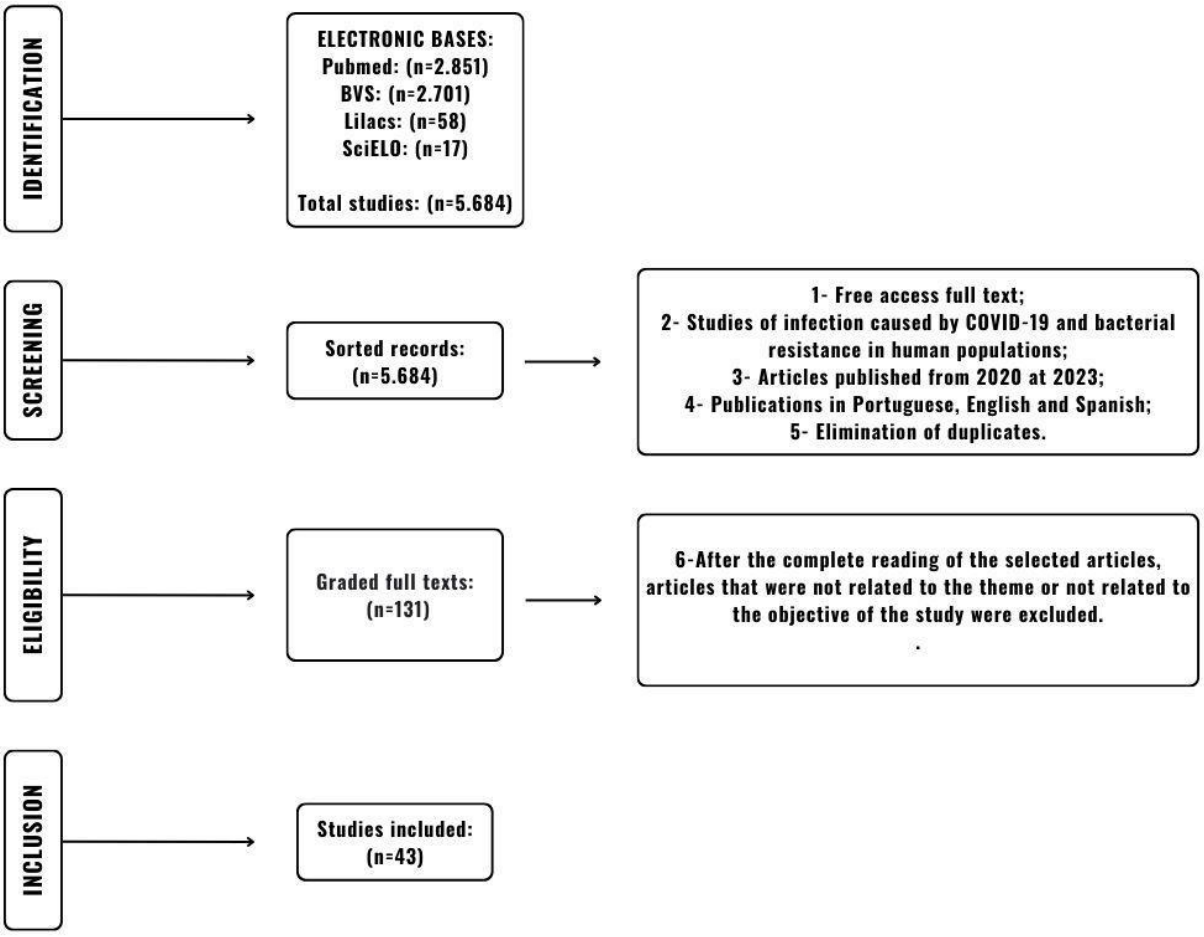
Figure 1. Sequence of steps performed to prepare this article.



Source: Created by the authors.

The criteria for identification, screening, eligibility and inclusion of articles are demonstrated in (Figure 2).

Figure 2. Sequence of criteria for identifying, screening, determining eligibility and including articles.



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RESULTS AND DISCUSSION

Table 1 - Articles that constituted the corpus of the integrative literature review

Author/Year	Title	Periodical	Objective	Resultados
Abrantes and Nogueira, 2021	Bacterial resistance to antimicrobials: a review of the main species involved in infectious processes	Brazilian Journal of Clinical Analyses	To execute a literature review study about the main bacteria involved in infectious processes, as well as to analyze the resistance of these microorganisms to antimicrobials. This study aimed to update the scientific community about a persistent public health issue that is bacterial resistance, and until then, does not have a definitive solution to its eradication.	Bacterial resistance was found at different levels in the studies included in this research, particularly against both emerging and well-established antimicrobials in clinical use, such as cephalosporins, carbapenems, quinolones, aminoglycosides, among others. Among the resistance mechanisms, we highlight the presence of extended-spectrum β-lactamases (ESBL), as well as carbapenem-resistant Enterobacteriaceae (CRE), methicillin-resistant Staphylococcus aureus (MRSA), and vancomycin-resistant Enterococcus (VRE).
Almeida *et al.*, 2023	Bacterial resistance: a global threat	Brazilian Journal of Health Review	To execute a narrative review study about the main bacterial resistance factors and to exploit strategies to fight it.	Bacterial resistance is critical, with both intrinsic and acquired resistance mechanisms developed by bacteria. The excessive and irrational use of antimicrobials contributes to the spread of these resistance mechanisms, including efflux pumps that reduce the concentration of the antibiotic within the bacterial cell.
Boechat *et al.*, 2023	Challenges in bacterial resistance associated with prevention management	Research, Society and Development	To execute an integrative review study about the main drivers	The indiscriminate use of antibiotics has compromised antimicrobial action, leading to the development of mechanisms that protect

			of bacterial resistance and to correlate with the main preventive measures.	bacteria. This occurs through spontaneous mutations and genetic recombination, which allow for genetic variation and result in the development of microbial resistance.
Brito *et al.,* 2020	COVID-19 pandemic: the biggest challenge for the 21st century	Health Surveillance under Debate: Society, Science & Technology	To execute a narrative review study about the aspects related to the etiology, clinical manifestations, diagnosis and treatment of COVID-19.	The articles highlighted that the origin of SARS-CoV-2, the causative agent of COVID-19, is uncertain. The rapid spread of the virus may be related to its mode of transmission and ability to survive in the external environment. Most hospitalized patients are over 60 years old, have immunosuppression, and comorbidities such as hypertension and diabetes. The diagnosis is primarily clinical and/or associated with molecular testing. There is no specific medication for the treatment of COVID-19. However, some drugs appear promising and are currently in clinical trial phases.
Castro *et al.,* 2021	Reduction in Life Expectancy in Brazil after COVID-19	Nature Medicine	To measure the decline of life expectancy at birth (e_0) and reduction in life expectancy at age 65 (e_{65}) in 2020 and in the first four months of 2021 due to the pandemic.	We estimate a decline in life expectancy at birth (e_0) in 2020 of 1.3 years, a level of mortality not seen since 2014. The reduction in life expectancy at age 65 (e_{65}) in 2020 was 0.9 years, bringing Brazil back to the levels of 2012. The decline was greater for men, widening the gap between women and men in e_0 by 9.1%. Among the states, Amazonas lost 60.4% of the improvements in e_0 since 2000. In the first 4 months of 2021, deaths from COVID-19 accounted for 107% of the total number in 2020. Assuming mortality rates had been the same as the all-cause rates from 2019 in the absence of COVID-19, COVID-19 deaths in

				2021 have already reduced life expectancy by 1.8 years, slightly higher than the estimated reduction for 2020 under similar assumptions.
Freires and Junior, 2022	Bacterial resistance to indiscriminate use of azithromycin versus Covid-19: an integrative review	Research, Society and Development	To execute an integrative review study about the azithromycin resistance promoted by the indiscriminate use of antibiotics during the COVID-19 pandemic.	The results show that self-medication during the pandemic period, particularly the indiscriminate use of azithromycin, has highlighted the factors contributing to this practice, which in turn leads to an increase in bacterial resistance. Factors such as errors in medical prescriptions, self-medication by the population, and ineffective regulation of antimicrobial sales in pharmacies and drugstores, where these medications are concentrated, contribute to bacterial multidrug resistance.
Pordanjani *et al.*, 2020	Aspects of Epidemiology, Pathology, Virology, Immunology, Transmission, Prevention, Prognosis, Diagnosis, and Treatment of COVID-19 Pandemic: A Narrative Review	International Journal of Preventive Medicine	To execute a review study about epidemiological, pathological, genetic, lethality, immunogenic, recovery, preventative, virulence, and transmission topics.	In general, it can be stated that mortality and the risk of fatality due to COVID-19 are higher in men, with increasing age, disease severity, systemic illness, as well as inadequate access to sufficient healthcare services.
Lazar *et al.*, 2023	Resistance, Tolerance, Virulence and Bacterial Pathogen Fitness—Current State and Envisioned Solutions for the Near Future	Pathogens	To assess the current level and meaning of bacterial resistance associated with virulence properties/aptitude and to review the main alternative or complementary	The current antibiotic crisis and the global phenomena of bacterial resistance both inherited and non-inherited and tolerance, particularly associated with biofilm formation, are leading to dire predictions of a post-antibiotic era in the near future. These forecasts point to increases in

			strategies to antibiotics, some of these already clinically applied or in clinical trials, others only planned or in the research phase.	morbidity and mortality rates as a result of infections caused by multidrug-resistant or pan-resistant microbial strains.
Mancuso *et al.*, 2021	Bacterial Antibiotic Resistance: The Most Critical Pathogens	Pathogens	To perform a review study about the antibiotic's mechanism of action and the resistance mechanisms of the commonly used antimicrobials. Furthermore, it discusses the current state of AMR in the most critical resistant bacteria, as determined by the WHO Global Priority Pathogens List.	Although antibiotic resistance is a natural process resulting from genetic changes in bacteria after exposure to antibiotics, this phenomenon is being accelerated by the excessive and improper use of antibiotics. Overuse of antibiotics kills susceptible bacteria and allows resistant bacteria to proliferate. Poor sanitation, inadequate infection control, and the use of antibiotics in farm animals are among the main reasons for the spread of antimicrobial resistance.
Mello and Oliveira, 2021	Challenges for adherence to bacterial resistance actions in large hospitals	Brazilian Journal of Nursing	To identify the challenges to actions to contain bacterial resistance.	Regarding healthcare professionals' knowledge about bacterial resistance prevention measures, 78.3% did not correctly describe the five moments of hand hygiene, and 76.6% did not correctly describe the measures for controlling bacterial resistance. Simple hand hygiene, followed by alcohol-based hand rub, was predominant (48.3%) among workers, and soap

				dispensers were located near alcohol dispensers in 58.3% of the nursing stations in healthcare units.
Miranda *et al.*, 2022	Consequences of inappropriate use of antibiotics: a literature review	Research, Society and Development	To execute a review study about scientific data regarding the associated consequences of the inadequate use of antibiotics.	The issue of bacterial resistance is associated with its indiscriminate and inappropriate use, leading to multidrug-resistant bacteria that are no longer sensitive to any type of substance. The impact of this resistance is collective and global, representing a threat to the continuity of life on the planet and constituting a significant public health problem worldwide. Therefore, it is crucial to minimize the emergence of antibiotic-resistant bacteria through more accurate prescriptions and better guidance for users on the prudent use of antibiotics.
Pakzad *et al.*, 2022	Worldwide prevalence of microbial agents' coinfection among COVID-19 patients: A comprehensive updated systematic review and meta-analysis	Journal of Clinical Laboratory Analysis	To execute a review study about the prevalence of pathogen coinfections among COVID-19 patients.	A total of 13,023 studies were found through systematic search. After a comprehensive analysis, only 64 studies with 61,547 patients were included in the study. The most common causative agents of co-infection among patients with COVID-19 were bacteria (combined prevalence: 20.97%; 95% CI: 15.95-26.46; I^2: 99.9%), while viral co-infections were less frequent (combined prevalence: 12.58%; 95% CI: 7.31-18.96; I^2: 98.7%). The combined prevalence of fungal co-infections was also 12.60% (95% CI: 7.84-17.36; I^2: 98.3%). Meta-regression analysis showed that sample size by age and WHO geographic region did not influence the heterogeneity.

Pereira *et al.,* 2020	Epidemiological, clinical and therapeutic aspects of COVID-19	Journal of Health Biological Science	To execute a review study about the epidemiological, clinical, and therapeutic aspects of COVID-19.	The COVID-19 pandemic is a major international test for the medical community, revealing weaknesses in the management of emerging viral diseases and reminding us that communicable diseases should never be underestimated or addressed with insufficient resources. The current situation also allows governments to assess their capabilities to organize human and material resources, share and analyze data in a timely manner, and cooperate with the media, journalists, and local communities to implement control activities.
Ukuhor, 2021	The interrelationships between antimicrobial resistance, COVID-19, past, and future pandemics	Journal of Infection and Public Health	To execute a review study on the main factors that influence the emergence of "superbugs" and the determinants of antimicrobial resistance.	There is evidence suggesting that factors such as the proliferation of counterfeit antimicrobials in some developing countries, international travel, issues with healthcare funding, misuse by humans and in agricultural production, and climate change are determinants of antimicrobial resistance (AMR) at various levels of society. These complex, interconnected determinants intersect with AMR in both current and past pandemics and may amplify the potential for a future antimicrobial resistance pandemic.
Wang *et al.,* 2020	The Characteristic of Virulence, Biofilm and Antibiotic Resistance of *Klebsiella pneumoniae*	International Journal of Environmental Research and Public Health	To conduct a review study on the virulence, biofilm, and tolerance to antibiotics mechanisms of *K. pneumoniae* and explore the application of whole genome	*K. pneumoniae* has recently become a notable virulent factor due to the increase in the number of patients with severe infections.

			sequencing and global proteomics, which will provide new options for the clinical treatment of *K. pneumoniae*.	
Zhang and Cheng, 2022	The Mechanism of Bacterial Resistance and Potential Bacteriostatic Strategies	Antibiotics	To conduct a review study about nine drug resistance mechanisms that promote the dissemination of drug-resistant bacteria (DRB) in the population. Subsequently, three types of potential antibacterial methods were also displayed, in which new antibacterial compounds have broad application prospects with different mechanisms of action.	Due to the widespread use of antibiotics, the environment in which bacteria live has changed drastically, leading to the selective survival of drug-resistant bacteria (DRB) that have adapted to the new environment. This "natural" selection will drive the bacterial population to evolve toward increased drug resistance.
Polly *et al.*, 2020	Impact of the COVID-19 pandemic on the incidence of multidrug resistant bacterial infections in an acute care hospital in Brazil	American Journal of Infection Control	The COVID-19 pandemic is correlated with an increase in the incidence density (ID) of carbapenem-resistant *Acinetobacter baumannii* (CRAB) and methicillin-resistant *Staphylococcus aureus* (MRSA), both in intensive care unit (ICU)	We identified 8,869 healthcare-associated infections (HCAI), of which 2,641 (29.7%) were caused by multidrug-resistant (MDR) bacteria, and 1,257 (14.1%) were from intensive care units (ICUs). The overall incidence of MDR infections increased by 23% ($P < 0.005$) during COVID-19. The general pathogen analysis showed significant increases in infections caused by CRAB and MRSA (+108.1%, $P < 0.005$; +94.7%, $P < 0.005$, respectively), but not in CRE, CRP, or VRE.

			environment and outside the ICU, and in the ID decrease of carbapenem-resistant *Enterobacterales* (CRE) and carbapenem-resistant *Pseudomonas aeruginosa* (CRP) in ICU environment.	In the ICU, the overall incidence of MDR infections decreased during COVID-19, but this decline was not significant (-6.5%, P = 0.26). Analysis of pathogen-specific infection rates in the ICU showed significant increases in CRAB and MRSA (+42.0%, P = 0.001; +46.2%, P = 0.04), significant reductions in CRE and CRP (-26.4%, P = 0.002; -44.2%, P = 0.003, respectively), and no change in VRE.
Dias *et al.*, 2021	Trend analysis of carbapenem-resistant Gram-negative bacteria and antimicrobial consumption in the postCOVID-19 era: an extra challenge for healthcare institutions	Journal of Hospital Infection	To identify the persistent clonal spread of CRAB with significant trend change after the COVID-19 pandemic. Carbapenem-resistant *K. pneumoniae* (CRKP) also showed a slight increase during the study time, but gradually, without detecting a trend change, which can be related to clonal spread.	The trend in the incidence density of carbapenem-resistant Gram-negative bacteria was analyzed in infections associated with devices and antimicrobial consumption in 99 intensive care units in a low-to-middle-income country from January 2019 to December 2020. The incidence of carbapenem-resistant *Acinetobacter baumannii* (CRAB) per 1,000 patient-days increased in 2020, and this finding had a strong positive correlation with the incidence density of COVID-19 according to the Spearman test. The consumption of polymyxin also increased in 2020, but without a significant correlation with the incidence density of CRAB or COVID-19, presumably due to empirical and non-targeted prescribing as a result of concerns about CRAB infections. These findings serve as a warning for infection control and antimicrobial stewardship programs.

Gaspar *et al.*, 2021	Pre- and post-COVID-19 evaluation of antimicrobial susceptibility for healthcare-associated infections in the intensive care unit of a tertiary hospital	Journal of the Brazilian Society of Tropical Medicine	The antimicrobial resistance increased during the pandemic, especially to *Klebsiella pneumoniae* isolates, with an increase in the resistance rate of Polymyxin B from 5% to 50%.	Antimicrobial resistance increased during the pandemic, particularly for isolates of *Klebsiella pneumoniae*, with a rise in the resistance rate from 5% to 50% for Polymyxin B.
Cureño-Díaz *et al.*, 2021	Impact of the modification of a cleaning and disinfection method of mechanical ventilators of COVID-19 patients and ventilator-associated pneumonia: One year of experience	American Journal of Infection Control	The implementation of cleaning and disinfection with enzymatic detergents/isopropyl alcohol of mechanical ventilators in patients with SARS-CoV-2 and ESKAPE bacteria had a positive impact on post-disinfection microbial contamination rates. *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and multidrug-resistant *Klebsiella pneumoniae* were the pathogens involved in the contamination cases. The pathogens were highly adhered to mechanical ventilators,	Contamination rates of 21.6% (n = 36) were identified in group A. The inspiratory branch was the circuit involved in most cases of post-disinfection contamination. *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and multidrug-resistant *Klebsiella pneumoniae* were the pathogens involved in these contamination cases. The pathogens were highly adherent, and in the case of *A. baumannii*, clonal dispersion was detected in 14 ventilators. Disinfection with enzymatic detergents achieved a 100% reduction in contamination rates.

			and in *A. baumannii*, clonal spread was detected in 14 ventilators. Disinfection with enzymatic detergents allows a 100% reduction in contamination rates.	
López-Jácome *et al.*, 2022	Increment Antimicrobial Resistance During the COVID-19 Pandemic: Results from the Invifar Network	Microbial Drug Resistance	The antimicrobial resistance increased in Mexico during the COVID-19 pandemic. The increase in oxacillin resistance in *S. aureus* and the carbapenem resistance in *K. pneumoniae* collected from blood samples was more significant. Furthermore, an increase was detected in erythromycin resistance in *S. aureus,* which can be associated with high use of azithromycin.	In the comparison between the second half of 2019 and the second half of 2020, increased resistance was detected in blood samples for *Staphylococcus aureus* to oxacillin (15.2% vs. 36.9%), erythromycin (25.7% vs. 42.8%), and clindamycin (24.8% vs. 43.3%) ($p \leq 0.01$). For *Klebsiella pneumoniae*, increased resistance was observed to imipenem (13% vs. 23.4%) and meropenem (11.2% vs. 21.4%) ($p \leq 0.01$). Increased resistance to ampicillin and tetracycline was detected for *Enterococcus faecium* ($p \leq 0.01$). For *Escherichia coli*, resistance was found to cefepime, meropenem, levofloxacin, and gentamicin ($p \leq 0.01$). For *Pseudomonas aeruginosa*, resistance was detected to piperacillin-tazobactam, cefepime, imipenem, meropenem, ciprofloxacin, levofloxacin, and gentamicin ($p \leq 0.01$).
Nori *et al.*, 2021	Bacterial and fungal coinfections in COVID-19 patients hospitalized during the New York City pandemic surge	Infection Control & Hospital Epidemiology	It was identified widespread use of antibiotics in most patients hospitalized	We observed bacterial or fungal co-infections in patients with COVID-19 admitted between March 1 and April 18, 2020 (152 out of 4,267, 3.6%). Among these patients, the mortality rate was

			with COVID-19 at New York City Medical Center. Bacterial and fungal co-infections occurred in <5%, but are of significant concern due to their occurrence in the most vulnerable patients. Furthermore, there was a worsening of the susceptibility profiles of emerging *Enterobacteriaceae* during the brief study period compared to antibiogram data from 2018 to 2019.	57%; 74% were intubated; 51% with bacteremia had central venous catheters. The time to culture positivity ranged from 6 to 7 days, and 79% had received antibiotics prior to culture. Co-infections by *E. cloacae* producing metallo-β-lactamase occurred in 5 patients.

Source: Created by the authors.

COVID-19 pandemic

January 30, 2020, the WHO announced that the outbreak of the new coronavirus SARS-CoV-2 constituted a Public Health Emergency of International Concern (PHEIC) and became the sixth in history in which a PHEIC was declared; moreover, this was the highest alert level of this organization because there is a risk of the disease, COVID-19, spreading to several countries, which requires global actions to be taken quickly and systematically (WHO, 2020).

The disease spread rapidly, and on March 11, 2020, the pandemic was declared by the WHO due to outbreaks in several countries, becoming a concern for the population and managers worldwide (Arruda *et al.,* 2021; WHO, 2023). In the Americas, according to the WHO, more than 190 million confirmed cases and 2 million deaths were registered (WHO, 2023).

The third continent had the highest number of confirmed cases, the first with the highest number of deaths. The five main countries on the American continent in relation to the number of confirmed cases are reported in (Table 1).

Table 1 - Number of confirmed cases and deaths due to COVID-19 according to American countries.

Country	Continent	No. of confirmed cases	No. of confirmed deaths
United States	North America	>100.000.000	>1.000.000
Brazil	South America	>37.000.000	>700.000
Argentina	South America	>10.000.000	>100.000
Mexico	North America	>7.000.000	>300.000
Colombia	South America	>6.000.000	>100.000

Source: WHO, data updated until 30/03/2024.

In general, the cases can be classified as follows: 1) asymptomatic: characterized by positive laboratory tests for the virus and lack of symptoms; 2) mild: characterized by the presence of nonspecific symptoms such as cough, sore throat and runny nose, followed by anosmia, ageusia, diarrhea, abdominal pain, fever, chills, myalgia, fatigue and/or cephalitis; 3) moderate: the most common symptoms can range from mild signs of the disease, such as persistent cough and daily persistent fever, to signs of progressive worsening of another symptom related to COVID-19 (adynamia, prostration, hyporexia, diarrhea), in addition to the presence of pneumonia without signs or severe symptoms; and 4) severe: considered severe acute respiratory syndrome presenting dyspnea/respiratory distress or persistent chest pressure with oxygen saturation less than 95% under ambient oxygen pressure or

bluish coloration of the lips or face. In children, the main symptoms include tachypnea, hypoxemia, difficulty breathing, an altered stage of consciousness, dehydration, difficulty eating, myocardial damage, increased liver enzymes, coagulation dysfunction, rhabdomyolysis, lethargy, seizures, and difficulty in feeding/food refusal. 5) Critical symptoms include sepsis, acute respiratory distress syndrome, severe respiratory failure, multiple organ failure, severe pneumonia, need for respiratory support and hospitalization in intensive care units (Brasil, 2022; CDC, 2022).

The following factors are considered possible complications of COVID-19 infection: 60 years or older, smoking status, obesity, different etiologies, arterial hypertension, cerebrovascular disease, severe or decompensated lung diseases (moderate/severe asthma, COPD), immunodepression and immunosuppression, advanced-stage chronic kidney disease (stage 3,4,5), diabetes mellitus, chromosomal diseases with an immunological fragility stage, malignant neoplasm (except nonmelanotic skin cancer), liver cirrhosis, hematological diseases and pregnancy (Pordanjani *et al.,* 2020).

SARS-CoV-2 can be identified by the following steps: I-molecular tests aimed at detecting the genetic material and SARS-CoV-2 ribonucleic acid (RNA) in respiratory tract samples via reverse transcription–quantitative polymerase chain reaction (RT–qPCR). To date, this technique remains the gold standard laboratory test for diagnosing COVID-19 in symptomatic patients in the acute phase (collected between the 1st and 5th days after the patient has started symptoms) (Brito *et al.,* 2020). In severe hospitalized patients, the sample can be collected through the 14th day after the patient has started to experience symptoms. II - Isothermal amplification tests can also identify the presence of SARS-CoV-2 RNA during the period of active infection. The main difference from RT–qPCR is that thermal amplification does not require the use of complex laboratory equipment or a real-time thermal cycler; thus, thermal amplification is a simpler technique. This methodology is being used in the Brazilian supplementary health system as an alternative to RT–qPCR since it is capable of efficiently and quickly detecting the SARS-CoV-2 virus in clinical samples. III - Rapid antigen detection test (RADT) are immunological tests that identify specific viral antigens, usually virus proteins. RADT is relatively simple compared to other available tests; moreover, most RADT tests do not require a complex laboratory structure and can be performed at the patient's place of care. RADT can be used to diagnose the acute

phase of the disease (between the 1st and 5th days after the patient becomes symptomatic) and is performed on different clinical samples (nasopharyngeal or nasal swabs), with results released in approximately 20 minutes. IV - different clinical tests can be used to determine aspects of the adaptive immune response and functionality of the antibodies produced against SARS-CoV-2. Tests for the detection of antibodies allow us to determine the serological profile of the population and identify the immunological response (antibody production IgA, IgM and/or IgG) of the individual to the SARS-CoV-2 virus; the main available methodologies since the beginning of the pandemic were enzyme immunoassays (enzyme-linked immunosorbent assays (ELISAs), chemiluminescence immunoassays (CLIAs) and electrochemiluminescence immunoassays (ECLIAs) (Brito *et al.,* 2020; Pakzad *et al*., 2022).

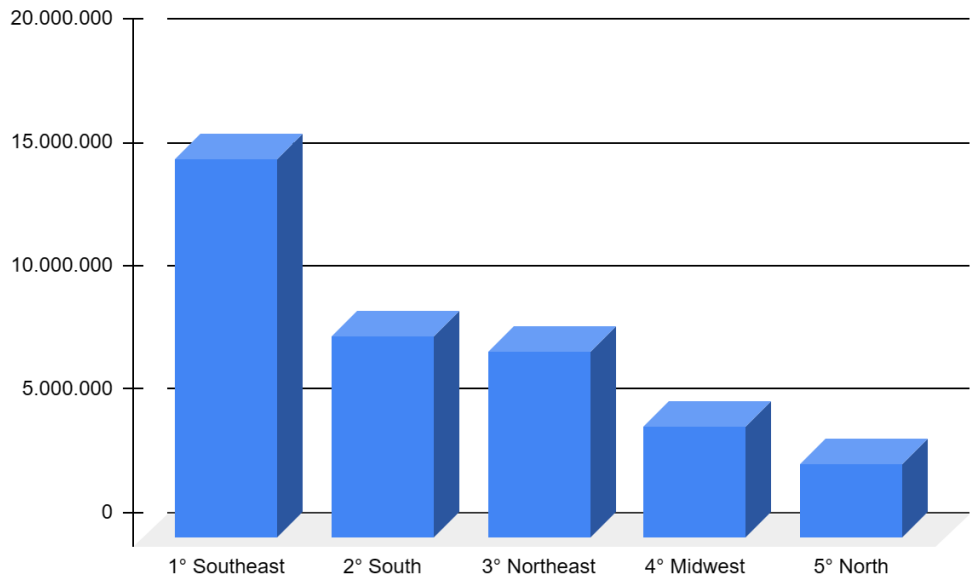
The COVID-19 pandemic in Brazil

Brazil is severely affected by COVID-19, with rapid spatial spread of confirmed cases and deaths (Pakzad *et al*., 2022). On February 26, 2020, Brazil reported its first COVID-19 case; as the first case in which the disease was detected in Latin America in less than 3 months, Brazil became the second most affected country by May 22, 2020, second only to the United States (Castro *et al*., 2021).

The regions of Brazil presented an elevated number of confirmed COVID-19 cases, especially in the southeastern region (Graphic 1). The most affected states of each region are São Paulo, in the Southeast, with more than 6 million confirmed cases; Rio Grande do Sul, in the South, with more than 3 million confirmed cases; Goiás, in the Midwest; Bahia, in the Northeast, with more than 1 million confirmed cases; and Pará, in the North, with more than 800 thousand confirmed cases (Pereira *et al.,* 2020).

On June 28, 2023, unfortunately, Brazil reached the milestone of 700 thousand deaths caused by COVID-19, a drastic number that comprises the biggest health crisis in the history of the country and reflects the magnitude of COVID-19 (Brasil, 2023).

Graphic 1 - Number of confirmed cases of COVID-19 according to region of Brazil.



Source: Ministério da saúde, data updated until 30/03/2024.

Antimicrobial resistance: a global threat

Bacterial infections have played an important role in the history of humanity. Since antiquity, various pathogenic bacteria have been found to be responsible for endemic and epidemic diseases that have disastrous effects on the human population. Since the end of the 19th century, the improvements in living conditions associated with environmental sanitation and, during the 20th century, the advent of antibiotics and vaccines have led to the belief that there was a way to definitively control these infections. However, recent events indicate that we are far from this long-awaited end because bacteria started again, even in developed regions of the world, to demonstrate their importance in morbimortality terms (Abrantes and Nogueira, 2021; Freires and Junior, 2022).

AMR is one of the 10 main threats to global health that humanity currently faces; it is becoming a serious health problem due to its significant economic and social impact and is one of the main causes of death worldwide. According to the Centers for Disease Control and Prevention (CDC) of the United States, more than 2.8 million antibiotic-resistant

infections occur in the U.S.A., and 35 thousand people die each year as a result (ANVISA, 2020; CDC, 2021).

Furthermore, the irrational use of antibiotics should occur not only among humans but also in the agricultural sector and veterinary medicine. Approximately 200 thousand to 250 thousand tons of antibiotics are estimated to be produced and consumed worldwide each year. Approximately 70% of these antimicrobial agents are consumed by animals, and 30% are consumed by humans. The estimated consumption of antimicrobial agents in agriculture worldwide varies between 63 thousand and 240 thousand tons each year due to scarce surveillance and data collection in many countries. Most antibiotics consumed by humans and animals are eliminated in the urine and feces and then enter sewerage systems, contaminating the environment. When exposed to antibiotics, bacteria that live in human or animal bodies can also develop resistance to antibiotics and spread to other people, as well as to the environment (WHO, 2020).

The microorganisms that represent an urgent threat to community health are as follows: Priority 1: Critical (carbapenem-resistant *Acinetobacter baumannii*, carbapenem-resistant *Pseudomonas aeruginosa,* carbapenem-resistant and extended-spectrum beta-lactamase-producing *Enterobacteriaceae* (ESBL-producing)); priority 2: high (vancomycin-resistant *Enterococcus faecium*, methicillin-resistant with intermediate resistance; vancomycin-resistant *Staphylococcus aureus*, clarithromycin-resistant *Helicobacter pylori*, fluoroquinolone-resistant *Campylobacter* spp., fluoroquinolone-resistant *Salmonella*, cephalosporin-resistant and fluoroquinolone-resistant *Neisseria gonorrheae*). Priority 3: medium (penicillin-nonsusceptible *Streptococcus pneumoniae*, ampicillin-resistant *Haemophilus influenzae*, fluoroquinolone-resistant *Shigella* spp.). The threat level of a bacterium is determined from the evaluation of its clinical and economic impact; projection of its 10-year incidence; transmissibility; effective antibiotics available; and forms of prevention (Almeida *et al*., 2020).

A forecast made by the World Bank Organization reviews the estimate that, in cases of high antimicrobial resistance incidence, there is an increase of 1.2 trillion dollars annually by the year 2050 in health investments. Given that the current economic model does not foresee large expenditures in this sector, financing that was before seeking poverty reduction would be used in the health industry. This factor would cause a decrease

in consumption and a consequent reduction in social welfare, with a decrease in the number of jobs and in government actions taken to reduce poverty, as well as the ability to force approximately 28 million people into a stage of extreme poverty when AMR (antimicrobial resistance) is not present (World Bank, 2021).

Studies indicate that the main difficulties in containing antibacterial resistance in hospitals are low adherence to hand hygiene, insufficient adherence to standard and contact precautions, lack of criteria for antibiotic prescription, difficulty with supplies and equipment, problems with scaling and rotating personnel, cleanliness of the environment, failures in the delivery of culture results by laboratories and indications of unnecessary invasive procedures (Wang *et al*., 2020; Mello and Oliveira, 2021).

Analyzing the context of AMR in public health, the WHO launched several programmes aimed at addressing this problem, with the goal of rationally using antimicrobial agents for human health, reducing infections through preventive measures, and educating individuals focused on raising awareness about the impact of bacterial resistance worldwide and encouraging research aimed at increasing investment in new medicine and health solutions (Boechat *et al.,* 2023).

Resistance mechanisms associated with antimicrobial therapy

During the first pandemic year, more than 29,400 people died from antimicrobial-resistant infections worldwide, commonly associated with health care. Nearly 40% of the people contracted the infection while in the hospital, proving that the threat of antimicrobial-resistant infections not only remains present but also represents a concerning scenario to human health. All these data allow us to deliberate on the harm caused by the pandemic, identifying clinical AMR strains and monitoring the growth of nosocomial resistance; these data are very important aspects of the current understanding of antibacterial resistance, given that the pandemic enables bacteria to easily spread and grow (CDC, 2021; CDC, 2022).

The AMR results from the ability of bacteria to mutate. These antibiotics confer protection against bacteria, decreasing the effectiveness of the antibiotics used to treat

infections. Due to the pandemic, there has been an increase in the prophylactic use of antimicrobial agents and the treatment of bacterial infections associated with COVID-19, as antimicrobial agents are able to directly interfere with the global spread of AMR due to exerted selective pressure (Boechat *et al.,* 2023; WHO, 2023).

Among the resistance mechanisms, permeability alteration, modified target sites, use of efflux pumps and production of enzymatic mechanisms are highlighted (Figure 3) (Boechat *et al*., 2023). One of the main resistance mechanisms is the alteration of cellular membrane permeability. Bacteria are capable of modifying the structure of the membrane, narrowing or blocking the pores where the antibiotic usually passes to the cell (ANVISA, 2020; Brasil, 2021).

Furthermore, bacteria can develop resistance through alteration of the antibiotic action site. This means that they modify the antibiotic target molecules, decreasing susceptibility to antibiotic effects. These modifications may occur through genetic mutations or the transfer of resistance genes from other bacteria (Lazar *et al.,* 2023).

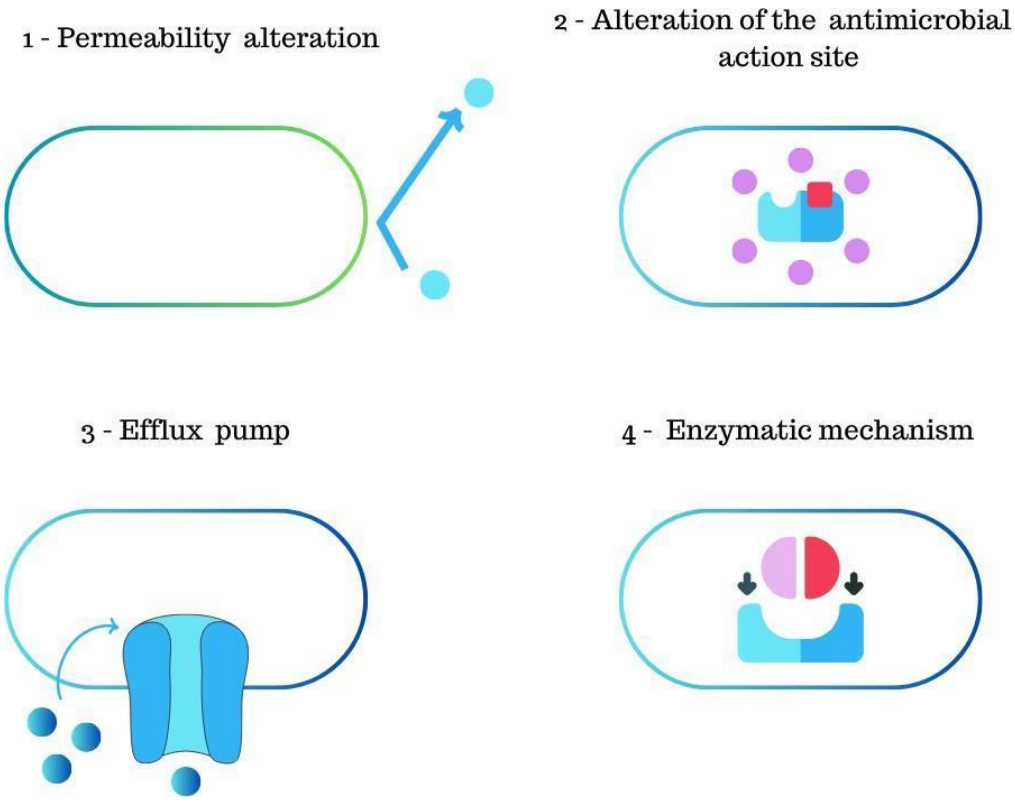
Another important mechanism is the presence of efflux pumps in the bacterial cell membrane. These proteins work as real pumps, expelling unwanted substances, including antibiotics, from the cell. When bacteria develop specific efflux pumps to antibiotics, they can expel these substances before they can act inside the cell, decreasing the effectiveness of the treatment (Mancuso *et al.,* 2021).

Finally, bacterial resistance can also occur through enzymatic mechanisms. The bacteria produce enzymes capable of inactivating or destroying antibiotics. These enzymes can break the drug in inactive parts, preventing its action or modifying its chemical structure, in such a way that it can no longer bind to the target molecules inside the bacteria (Mancuso *et al.,* 2021).

Bacterial resistance is a growing and concerning problem that occurs when bacteria develop the ability to survive and multiply in the face of antibiotic use. This resistance may occur through many simultaneous mechanisms, which makes it more difficult to combat bacteria with available antibiotics. Therefore, the conscious and rational use of antibiotics is extremely important for preventing the development of this disease. Furthermore, it is necessary to develop new therapeutic strategies to combat these resistant bacteria. The

resistance mechanisms are complex and involve many molecular interactions. Therefore, knowledge about these mechanisms is fundamental to the development of more effective strategies to combat antimicrobial-resistant bacterial infections (Zhang and Cheng, 2022).

Figure 3. Mechanisms of bacterial resistance.



Source: Created by the authors.

The excessive or unnecessary use of antimicrobial agents may result in potentially serious consequences for health since these agents can cause pharmacological toxicity in different human tissues (Miranda *et al.*, 2022). Moreover, resistance to antibiotics is driven by the abuse and unnecessary use of these medicines, as well as by the lack of adequate prevention and control of infections. It is important to emphasize that Brazil has one of the highest rates of antibiotic consumption among American countries, with available data, second only to countries such as Mongolia, Turkey, France and the United Kingdom (Ukuhor, 2021). Therefore, it is necessary to take effective measures to increase public

awareness about the responsible use of antimicrobial agents and to promote adequate practices for the prevention and control of infection.

Brazil and America: the challenges of antimicrobial resistance in the pandemic scenario

The COVID-19 pandemic has played an important role in increasing AMR worldwide. A study carried out in Brazil by Polly and collaborators (2022) evaluated the incidence density and revealed a significant increase in infections caused by MDR compared to that in the prepandemic and pandemic periods, both in ICUs and other hospital units. In internal medicine, nursing and intermediate care units, the microorganisms that exhibited significant increases in resistance were carbapenem-resistant *Enterobacteriaceae* (>6,5%), carbapenem-resistant *A. baumannii* (>108.1%), and methicillin-resistant *S. aureus* (MRSA) (>94.7%); for infections in ICU patients, carbapenem-resistant *A. baumannii* (>42.0%) and MRSA (>46.2%) were found (Polly *et al.*, 2022).

Similarly, another study conducted in Brazil by Dias and collaborators (2021) revealed a significant increase in infections by carbapenem-resistant *A. baumannii* (>4,5%) compared to prepandemic and pandemic periods (Dias *et al.,* 2021). This increase in bacterial resistance highlights the potential of these pathogens to adapt to the nosocomial environment and, consequently, the ease of dissemination and persistence of hospital stay. The studies cited above are crucial to epidemiological monitoring to understand the adaptation and behavior of AMR in Brazil in relation to the nosocomial environment.

Gaspar and collaborators (2021), observed in clinical isolates from Brazil that *A. baumannii* showed the highest rate of carbapenem resistance, reaching an incredible 78,6%. The resistance rate of *Klebsiella pneumoniae* to polymyxin B increased to 15%. When considering only the isolates resistant to both carbapenems and polymyxin B, the resistance rate reached 24.1%. Notably, during 2020, the resistance rates of both *A. baumannii* resistant to carbapenems and carbapenem-resistant *Klebsiella pneumoniae* increased significantly. Furthermore, the incidence density of carbapenem-resistant *Klebsiella pneumoniae* also considerably increased during the pandemic compared to that in the prepandemic period (Gaspar *et al.*, 2021).

In Mexico, several epidemiological studies were conducted, including one carried out by Cureño-Díaz and collaborators (2021). In this study, several methods of disinfection were applied to mechanical ventilation, and prolonged resistance was observed in *A. baumannii, P. aeruginosa* and *K. pneumoniae* strains to the disinfection method "A", superoxidation/cl-isopropyl alcohol, and 36 bacterial strains were detected isolated from mechanical ventilation after disinfection, with *A. baumannii* accounting for 38.88% of the cases, *P. aeruginosa* accounting for 33.33% and *K. pneumoniae* accounting for 27.77%. Method "B", which used an enzymatic detergent and isopropyl alcohol, was 100% effective, and no bacterial strains were detected after disinfection (Cureño-Díaz *et al*., 2021). Furthermore, the study involved epidemiological monitoring but also presented a flaw in infection control and disinfection processes, considering that the "A" method used was not effective for the clinical strains mentioned above and strengthening the importance of understanding the difficulties in the containment of bacterial spread so that government programs can be applied with a focus on prevention, social awareness and stricter nosocomial internal conduct. Additionally, the persistence of the *A. baumannii* strain, the most common microorganism in clinical specimens, is extremely important because of its strong adaptability and persistence in the nosocomial environment.

López-Jácome and collaborators (2022) provided concerning data about bacterial resistance to antibiotics during the Mexico pandemic. These data highlight the importance of understanding the excessive use of antibiotics during this period and the consequences of this overuse. An increase in resistance to oxacillin, levofloxacin, erythromycin and clindamycin was observed in *S. aureus* strains. Moreover, increased resistance to ampicillin and tetracycline has been reported in *E. faecium*, and increased resistance to cefoxitin, cefepime, imipenem, meropenem and levofloxacin has been reported in *K. pneumoniae.* Regarding the *E. coli* samples, there was an increase in resistance to practically all the antimicrobial agents evaluated, including ampicillin-sulbactam, ampicillin, cefoxitin, ceftazidime, cefepime, imipenem, meropenem, ciprofloxacin, levofloxacin, gentamicin and trimethoprim-sulfamethoxazole. Among the *A. baumannii samples,* greater resistance to piperacillin-tazobactam, imipenem, meropenem, ciprofloxacin, levofloxacin and gentamicin was observed. With respect to *P. aeruginosa*, increasing rates of resistance to piperacillin-tazobactam, cefepime, imipenem, meropenem, ciprofloxacin and levofloxacin have been recorded. These results are extremely scientifically relevant and lead to

questions about the therapeutic resources available for combating bacterial resistance (López-Jácome *et al.,* 2022).

Furthermore, these data complement the findings of other studies related to the subject. For example, a study executed in the USA by Nori and collaborators (2021) also provided data about the use of antibiotics during the pandemic. In this study, of the 5,853 patients with COVID-19 admitted between March 1st and May 31st from 2020, 4,130 patients (71%) received at least one antibiotic. The most commonly used agents were doxycycline, azithromycin, levofloxacin, ciprofloxacin, ceftriaxone, cefepime, intravenous vancomycin and piperacillin/tazobactam. Notably, levofloxacin was administered to 71% of admitted patients (Nori *et al.* 2021).

CONCLUSION

This study confirms the increase in bacterial resistance during the COVID-19 pandemic, strongly influenced by factors such as prolonged hospitalizations and the reduction in available therapeutic options, which contributed to the spread of bacterial infections in hospital environments. Inappropriate and excessive use of antibiotics, combined with failures in control and disinfection methods, exacerbated the issue of microbial resistance, making the treatment of nosocomial infections increasingly challenging.

It is crucial for future research to focus on identifying gaps in infection prevention and control programs, as well as estimating the investments needed for developing new therapeutic options. Continuous monitoring of antibiotic use and the implementation of effective strategies to curb the spread of bacterial resistance are essential to combat this growing problem. This study underscores the need for coordinated global actions to address bacterial resistance, a challenge that has intensified in the pandemic context.

AUTHOR CONTRIBUTIONS

Rhaldney Kaio Silva Galvão, Lara Limeira de Oliveira, Sérgio Dias da Costa Júnior e Isabella Macário Ferro Cavalcanti: participated in all stages, from the design of the review study to the final version of the article.

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