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Rua Fernando Abott, 174 - 2º andar - Bairro Centro – Santa Cruz do Sul/RS - CEP 96810-150
TELEFONE/FAX: 051 3713.7484 / 3713.7449 / E-MAIL: reci@hotmail.com
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Hospital Santa Cruz

ORIGINAL ARTICLE

Analysis of antifungal prescriptions in a Basic Health Unit in the Federal District

Análise de prescrições de antifúngicos em uma Unidade Básica de Saúde do Distrito Federal

Análisis de prescripciones de antifúngicos en una Unidad Básica de Salud del Distrito Federal

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Corresponding Author:
Débora Santos Lula Barros
deborasantoslulabarros@gmail.com

Address: QS 402 conjunto A lote 1 apartamento 301, Samambaia Norte, Brasília, Distrito Federal, Brasil.

Débora Santos Lula Barros[1];
Pedro Juan Ribeiro Calisto dos Santos[2];
Thayanne Nara da Rocha[3];

[1] *University of Brasília, Brasília, Federal District, Brazil.*
[2] *Catholic University of Brasília, Brasília, Federal District, Brazil.*
[3] *Federal District Department of Education, Brasília, Federal District, Brazil.*

ABSTRACT

Background and Objectives: the inappropriate use of antifungal agents leads to the development of resistance and a lack of treatment effectiveness, which can result in the worsening of clinical condition, persistent infections, increased hospitalization rates and prolonged hospital stays as well as deaths and higher healthcare costs. This study aimed to analyze antifungal prescriptions in a Basic Health Unit in the Federal District Southern Health Region, Brazil. **Methods:** this was a cross-sectional, descriptive, and observational study, in which the duplicate copies of prescriptions retained at the pharmacy were assessed. **Results:** a total of 69 prescriptions dispensed in October 2019 were analyzed. Concerning medication prescription according to the Brazilian Common Denomination (DCB) and the verification of the presence of antifungal agents in the Federal District's List of Essential Medications (REME-DF), rates above 90% were found in the analyzed documents. Only one prescription contained the combination of two antifungal agents. The predominant prescribing category was nursing, followed by physicians and dentists. The most prescribed antifungal agents were fluconazole and miconazole. The routes of administration present in prescriptions were oral and topical. **Conclusion:** the lack of studies on antifungal use in primary care highlights the importance of this investigation for producing specialized knowledge on the subject.

Keywords: *Antifungal Agents. Primary Healthcare. Drug Utilization. Pharmacoepidemiology.*

RESUMO

Justificativa e Objetivos: o uso inadequado de agentes antifúngicos acarreta o desenvolvimento de resistência e a falta de efetividade do tratamento, o que pode levar ao agravamento do quadro clínico e à persistência das infecções, ao aumento das taxas e à prolongação das internações hospitalares, além de óbitos e elevação dos custos em saúde. O presente estudo teve como objetivo analisar as prescrições de antifúngicos em uma Unidade Básica de

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Saúde da Região de Saúde Sul do Distrito Federal, Brasil. **Métodos:** trata-se de estudo transversal, descritivo e observacional, no qual foram avaliadas as segundas vias das prescrições retidas na farmácia. **Resultados:** foram analisadas 69 prescrições dispensadas em outubro de 2019. Em relação à prescrição de medicamentos segundo a Denominação Comum Brasileira (DCB) e à verificação da presença dos antifúngicos na Relação de Medicamentos Essenciais do Distrito Federal (REME-DF), encontraram-se taxas superiores a 90% nos documentos analisados. Apenas uma prescrição continha a associação de dois antifúngicos. A categoria prescritora predominante foi a enfermagem, seguida por médicos e odontólogos. Os antifúngicos mais prescritos foram fluconazol e miconazol. As vias de administração presentes nas prescrições foram oral e tópica. **Conclusão:** a escassez de estudos sobre o uso de antifúngicos na atenção primária ressalta a importância desta investigação para a geração de conhecimento especializado sobre o tema.

Descritores: *Antifúngicos. Atenção Primária à Saúde. Uso de Medicamentos. Farmacoepidemiologia.*

RESUMEN

Justificación y Objetivos: el uso inadecuado de agentes antifúngicos provoca el desarrollo de resistencia y la falta de efectividad del tratamiento, lo que puede llevar al agravamiento del cuadro clínico, infecciones persistentes, aumento de las tasas y prolongación de las hospitalizaciones, además de muertes y mayores costos en salud. El presente estudio tuvo como objetivo analizar las prescripciones de antimicóticos en una Unidad Básica de Salud de la Región Sanitaria Sur del Distrito Federal, Brasil. **Métodos:** se trata de un estudio transversal, descriptivo y observacional, en el que se evaluaron las segundas copias de las prescripciones retenidas en la farmacia. **Resultados:** se analizaron un total de 69 prescripciones dispensadas en octubre de 2019. En cuanto a la prescripción de medicamentos según la Denominación Común Brasileña (DCB) y la verificación de la presencia de antifúngicos en la Relación de Medicamentos Esenciales del Distrito Federal (REME-DF), se encontraron tasas superiores al 90% en los documentos analizados. Solo una prescripción contenía la combinación de dos agentes antifúngicos. La categoría prescriptora predominante fue enfermería, seguida por médicos y odontólogos. Los antifúngicos más prescritos fueron fluconazol y miconazol. Las vías de administración presentes en las prescripciones fueron oral y tópica. **Conclusión:** la falta de estudios sobre el uso de antifúngicos en la atención primaria destaca la importancia de esta investigación para la producción de conocimiento especializado sobre el tema.

Palabras Clave: *Antifúngicos. Atención Primaria de Salud. Utilización de Medicamentos. Farmacoepidemiología.*

INTRODUCTION

The Basic Health Unit (BHU), according to Ordinance 2,436 of September 21, 2017, is any healthcare establishment that provides primary care actions and services within the Brazilian Health System (In Portuguese, *Sistema Único de Saúde* - SUS).[1]

Primary healthcare (PHC), in turn, is described as the set of individual, family and collective health actions that involve promotion, prevention, protection, diagnosis, treatment, rehabilitation, harm reduction, palliative care and health surveillance. To this end, PHC is developed through integrated care practices and qualified management, which necessarily includes multidisciplinary teamwork aimed at the population of a defined territory, over which these professionals take health responsibility.[1,2]

In addition to being the preferred gateway to the SUS, PHC also acts as the organizer of the Healthcare Networks (In Portuguese, *Redes de Atenção à Saúde* - RAS) and as the coordinator of care. Thus, it is responsible for both the chronic monitoring of users in its territory and individuals who arrive spontaneously with acute conditions. When necessary, cases that cannot be treated properly are referred to the corresponding level of healthcare.[1-7]

The PHC pharmacist carries out both technical-managerial activities, promoting the regular supply and adequate storage of medications and supplies, as well as technical-pedagogical and clinical-assistance activities, offering pharmaceutical care to users and providing health education for the multidisciplinary team and the population.[8-10]

Pharmacological treatment is the most widely used treatment to combat acute and chronic infectious diseases. Thus, antimicrobial drugs play an important role in restoring and improving users' health. However, on the other hand, their indiscriminate and inappropriate use poses a risk not only to individuals but also to society.[11,12]

Fungal infections treated in PHC in Brazil, especially superficial ones such as candidiasis, dermatophytosis and pityriasis versicolor, are prevalent, with rates that can vary between 10% and 30% in populations treated at this level of healthcare. These cases occur more frequently in vulnerable populations, such as children, older adults, immunocompromised patients and people with chronic diseases such as diabetes mellitus. The prevalence of these infections varies according to social determinants of health, such as hygiene, socioeconomic conditions and access to healthcare services and technologies, which makes primary care crucial for early diagnosis and effective treatment.[11-13]

Inappropriate use of antifungal agents leads to the development of resistance and, as a consequence, can

worsen clinical conditions and cause persistent infections, in addition to reducing quality of life, prolonging hospital stays, increasing mortality and healthcare costs.[12,13]

Drug utilization studies provide fundamental theoretical support for the planning, development and assessment of pharmaceutical care in PHC. Considering this context, the present research aimed to analyze antifungal prescriptions in a BHU in the Federal District Southern Health Region, Brazil.

METHODS

This is a cross-sectional, descriptive and observational study, in which second copies of prescriptions from the pharmacy of BHU nº 03 in Santa Maria, Federal District, Brazil were assessed.

The Federal District has 31 satellite cities. Santa Maria, one of these satellite cities, has an estimated population of 130,000 inhabitants. The city has 12 BHUs that offer primary care, including medical consultations, nursing, pharmacy services and monitoring of chronic diseases. Moreover, there is the *Hospital Regional de Santa Maria*, which provides emergency services and specialized care. BHU nº 3 in Santa Maria, where the study was conducted, assists predominantly the urban population due to its location.

To perform the analysis of prescriptions, the following inclusion criteria were adopted: documents that contained at least one drug from the antifungal class and whose drug supply by the pharmacy occurred in October 2019. The exclusion criterion for the prescriptions was illegibility of documents.

Data collection was carried out manually in the following month, i.e., in November 2019. It is important to note that the BHU pharmacy does not operate on weekends and, therefore, only the documents dispensed on weekdays were analyzed. It is estimated that a total of 1,500 prescriptions are dispensed per month at the unit.

Considering the compliance of prescriptions with the indicators of rational use of medications proposed by the World Health Organization, the criteria analyzed were: whether antifungal agents were prescribed as monotherapy or in combination; whether the Brazilian Common Denomination (In Portuguese, *Denominação Comum Brasileira* - DCB) was used; the definition of administration route; whether or not the drug is present in the Federal District's List of Essential Medications (In Portuguese, *Relação de Medicamentos Essenciais do Distrito Federal* - REME-DF); and the identification of the prescriber's professional category. REME-DF is the reference document for all services provided in the satellite cities of the Federal District. Due to the constant review of REME-DF, its latest version available on the Federal District Department of Health website was consulted.

For data organization and processing, the Office for Windows data package was used through the Excel® tool, producing descriptive statistics data. Finally, the project was submitted and approved by the Health Sciences Teaching and Research Foundation (In Portuguese, *Fundação de Ensino e Pesquisa em Ciências da Saúde*) Research Ethics Committee (REC), under Opinion 3,142,346 and Certificate of Presentation of Ethical Appreciation 99335218.2.3001.5553, in accordance with guidelines proposed in the Ministry of Health Resolutions 466/2012, 510/2016 and 580/2018. Furthermore, all documents of the scientific project related to the REC approval were presented to the BHU managers and pharmacist studied before data collection.

RESULTS

In the study, 69 (5.6%) prescriptions containing antifungal agents were identified out of a total of 1,231. Most of prescribed medications belonged to REME-DF, i.e., 65 medications (94.21%). Most of medications were prescribed by DCB (97%).

As for the number of medications per prescription, 98.55% (n=68) of these documents contained only one prescribed antifungal. The only association found was between tioconazole and tinidazole. The most prescribed antifungal agents were fluconazole (52.17%) and miconazole (37.7%) (Table 1).

Table 1. Antifungal agents prescribed in a Basic Health Unit in Federal District, Brazil.

Antifungal agents	N (%)
Fluconazole	36 (52.17%)
Miconazole	26 (37.70%)
Ciclopirox olamine	3 (4.34%)
Itraconazole	2 (2.89%)
Ketoconazole	1 (1.45%)
Tioconazole + tinidazole	1 (1.45%)
Total	69 (100%)

Source: own authorship.

The main route of administration of studied drugs, considering all prescribed antifungal agents, was oral (55.07%), followed by topical (44.93%).

Regarding the provider's professional category, most prescriptions were written by nurses (53.6%), followed by physicians (45%) and, finally, dentists (1.4%).

DISCUSSION

Prescription analysis studies allow for a better assessment of the profile of medication use and provide evidence on population consumption, assisting in the planning of actions and services, in addition to revealing the priorities that should be considered strategic in healthcare and assistance qualification.[3]

According to the documents analyzed, no prescriptions were excluded due to lack of legibility, which is a positive indicator according to theoretical assumptions

of safe and rational use of medications. It is worth remembering that this result differs from that found in most studies conducted in Brazil, since the literature indicates that it is still common to find incomplete or incomprehensible prescriptions, including weaknesses in the identification of patients, professionals and the prescribed drug technology.[11]

Similar to the value found in this study, a study that aimed to analyze prescriptions of antihypertensives in a BHU in the Federal District found a rate of 91.1% of medications present in REME-DF. Prescribing medications included in the essential medications list is advantageous, as it enables access to health technologies available in the SUS.[3,14-15]

According to the theoretical arsenal of rational use of antimicrobial agents, it is essential to prioritize the use of monotherapy, as was found in most prescriptions of antifungal agents analyzed. The scientific literature highlights the importance of reserving combinations of antimicrobial agents for more complex and resistant conditions, when synergism is crucial for the treatment of infections and for cases of polymicrobial infections.[3,16,17]

Furthermore, the rational and cautious use of antifungal agents is essential to avoid clinically relevant drug interactions, prevent the development of resistance and minimize the risk of adverse effects, among other outcomes. Antifungal agents often interact with other drugs due to their influence on hepatic metabolism, especially through cytochrome P450. These interactions can alter the levels of other medications, increasing the risk of adverse effects or reducing the effectiveness of treatment, which requires careful monitoring. Therefore, avoiding overprescription of medications is crucial.[16,17]

The present investigation found rates close to 100% of antifungal agents prescribed according to DCB, which represents a positive indicator of good prescribing practices. A study that aimed to assess and compare the quality of antibiotic prescriptions dispensed in a public pharmacy and in a private pharmacy revealed that, of the 476 prescriptions in the public pharmacy, 82% of antibiotics were expressed according to DCB.[18]

Similar to the present investigation, a study that investigated prescriptions of antihypertensives in a BHU in the Federal District found a rate higher than 90% in relation to the DCB adoption indicator. Prescribing medications according to DCB is essential, as it facilitates access to medications, whether through purchase or free of charge through healthcare services.[3,19]

Similar to the data presented in Table 1, a study conducted in a hospital in Oman in 2013, through the analysis of 1,353 prescriptions, revealed that fluconazole was the most prescribed antifungal (n=715; 52.8%), followed by nystatin and voriconazole (n=233; 17.2% and n=152; 11.2%, respectively). Fluconazole is an antifungal from the azole group widely used due to its long half-life, good tolerability by users and minimal associated toxicity.[13]

A study conducted in a city in São Paulo aimed to describe the practice of prescribing, dispensing, using, adhering to and storing medications by older adults in Family Health Strategy units. Among the prescribed medications, some classes were less used, such as antilipemic drugs (62.1%), nutrients (50%), herbal medicines or medicinal herbs (28%), antimycotic and antifungal agents (25%), and antimicrobial agents (21.4%). In the group of antimycotics and antifungal agents, ketoconazole and fluconazole were identified as the prevalent medications.[14]

Fungal diseases range from superficial infections, such as cutaneous and subcutaneous infections, to systemic conditions. Scientific literature highlights that, considering the rise in resistance to antifungal agents over time, rational prescription of these drugs is crucial, even if it is topical. Furthermore, from the point of view of rational use indicators, the oral route hegemony is desirable, since this is considered a safe route when compared to parenteral routes. Therefore, considering the aforementioned administration data route, even though the routes used in the prescription of BHU antifungal agents are considered safe, such as oral and topical administration, it is necessary to use this class of drugs cautiously and consciously, mainly due to the increase in cases of resistance.[12,13,21,22]

One result that differs from this study in relation to others conducted in the PHC of the Federal District is the prescribing category, which, as observed in the results, has a higher prevalence of nursing. The supremacy of medicine in prescribing medications is evident, not only in primary care, but also in the various levels of healthcare. One possible explanation for the results found is a greater appreciation of nursing as a category of prescribing medications in PHC in recent years, not only in the Federal District, but it is a phenomenon that is also evident in other Federative Units of Brazil. Nursing prescription is a legal duty of nurses that must be carried out within the limits of their training and competency. In general, nurses can prescribe medications according to the SUS and Ministry of Health clinical protocols and therapeutic guidelines, requiring ongoing education to ensure care efficacy and effectiveness.[3,23,24]

Furthermore, still in the wake of the aforementioned discussion, to ensure the resolvability and effectiveness of actions and services, constant training on the topic of promoting the rational use of antifungal agents in favor of preventing medication errors is essential for all professional categories involved in prescribing PHC medications so that unique and contextualized educational actions are developed according to each profile of occupational assignment/performance.[25,26]

Still on the importance of continuing education in favor of the rational use of antifungal agents, it is highlighted that it is essential that healthcare professionals participate in qualifications related to laboratory tests for differential diagnosis. Diagnostic confirmation of mycological diseases is crucial to avoid inappropriate treatments, which not only compromise therapeutic effectiveness but also contribute to the development of antifungal resistance. Furthermore, many lesions caused by fungi present clinical characteristics similar to those of lesions of other etiologies, which highlights the need for a careful diagnostic approach. In this regard, training actions focused on the

use of specific tests in the diagnostic process are essential to ensure accuracy in clinical management, promoting better outcomes for patients and reducing the impacts of resistance in the context of public health.[27]

One limitation to be highlighted in this study is the time of data collection. Due to the emergence of the coronavirus disease 2019 (COVID-19) pandemic, the researcher was authorized to collect data for a reduced period to avoid crowding in the small physical space of BHU. Therefore, the investigation covered only the data generated in October 2019. As a result, the data may be underestimated, highlighting the importance of conducting scientific investigations with longer collection periods. Furthermore, due to its retrospective nature, the study faces limitations related to old data, which may be inaccurate, incomplete and outdated. Finally, local studies may face the limitation of the lack of generalizability of results to other populations, due to the local context's specific characteristics.

Furthermore, it is worth remembering that the scarcity of studies on the use of antifungal agents at different levels of healthcare in Brazil and worldwide makes it difficult to conduct a comparative discussion of the findings of this study with others that had a similar objective. The few studies found addressed the use of antifungal agents in hospital settings or discussed consumption data for the category of antimicrobial agents in general in primary care. Thus, the present investigation is relevant and contributes to the production of specialized knowledge on the subject.

The research highlighted a predominantly rational practice in the prescription of antifungal agents in the studied BHU. The high rate of compliance with REME-DF, the use of DCB, the prescription in monotherapy and the choice of safe administration routes suggest an effective approach to promote the safe and rational use of these drugs. The predominance of prescriptions by nurses indicates a growing appreciation of this category, although ongoing training is still needed to improve practice over time. Despite the study's temporal and contextual limitations, its value in filling a gap in research on antifungal agents stands out, contributing significantly to the understanding and improvement of prescribing practices in primary care.

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AUTHORS' CONTRIBUTIONS

Débora Santos Lula Barros contributed to bibliographic research, abstract writing, introduction, methodology, discussion, interpretation and description of results, preparation of tables, conclusions, review and statistics. **Pedro Juan Ribeiro Calisto dos Santos** contributed to work review. **Thayanne Nara da Rocha** contributed to work review.

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ORIGINAL ARTICLE

HIV/AIDS cases and deaths in Brazil, 2000 to 2019: a spatial analysis

Casos e óbitos de HIV/AIDS no Brasil, 2000 a 2019: uma análise espacial

Casos y muertes por VIH/SIDA en Brasil, 2000 a 2019: un análisis espacial

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Corresponding Author:
Isadora Sabrina Ferreira dos Santos
isadorasabrina18@gmail.com

Address: Instituto Aggeu Magalhães – Av. Professor Moraes Rego, s/n, Cidade Universitária, Recife, Pernambuco, Brasil.

Isadora Sabrina Ferreira dos Santos[1];
Laís Eduarda Silva de Arruda[1];
José Thiago de Lima Silva[2];
Guilherme Lira[3];
Emília Carolle Azevedo de Oliveira[1];

[1] *Fundação Oswaldo Cruz, Instituto Aggeu Magalhães, Recife, PE, Brazil.*
[2] *Universidade Federal de Pernambuco, Centro Acadêmico de Vitória, Vitória de Santo Antão, PE, Brazil.*
[3] *Universidade Federal de Pernambuco, Recife, PE, Brazil.*

ABSTRACT

Justification and Objectives: although there has been progress in antiretroviral treatment and advances in preventive campaigns, cases and deaths from HIV/AIDS persist today, reflecting a serious public health concern. This study aimed to carry out a spatial analysis of cases and deaths due to HIV/AIDS in Brazil, 2000-2019. **Methods:** this is a cross-sectional, ecological study. The data were extracted from the Notifiable Diseases Information System and the Mortality Information System. To identify spatial distribution patterns and possible clusters, Kernel maps and Local and Global Moran's Index of prevalence and mortality were created in TerraView and QGIS. **Results:** during the period of this study, there were 756,586 cases and 232,892 deaths from HIV/AIDS, with the highest concentrations of cases in the states of São Paulo and Rio de Janeiro and deaths in Rio Grande do Sul and Rio de Janeiro. In Kernel, there was high density in the Southeast, South and Northeast, mainly in Rio Grande do Sul, Rio de Janeiro and Santa Catarina, for the mortality rate. Meanwhile, in Local Moran's Index, high-value clusters are in the Southeast, South and Midwest, which are also the locations for the mortality rate. **Conclusion:** cases were concentrated in the state of São Paulo and Rio de Janeiro, while mortality rates reached higher density in Rio Grande do Sul and Rio de Janeiro. These findings point to the need for regional coping strategies, such as strengthening educational and prevention campaigns.

Keywords: *HIV. Acquired Immunodeficiency Syndrome. Public Health. Ecological Studies. Spatial Analysis.*

RESUMO

Justificativa e Objetivos: embora houvesse evolução no tratamento com antirretrovirais e avanços nas campanhas preventivas, os casos e mortes de HIV/AIDS hodiernamente persistem, refletindo-se em um grave problema de saúde pública. O objetivo deste estudo é realizar uma análise espacial dos casos e óbitos por HIV/AIDS no Brasil, 2000-2019. Métodos: trata-se de estudo transversal, ecológico. Os dados foram extraídos do Sistema de Informação

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de Agravos de Notificação e do Sistema de Informação de Mortalidade. Para identificar padrões de distribuição espacial e possíveis clusters, realizaram-se mapas de Kernel e Índices Local e Global de Moran da prevalência e mortalidade no *TerraView* e QGIS. **Resultados:** no período deste estudo, ocorreram 756.586 casos e 232.892 óbitos de HIV/AIDS, com maiores concentrações dos casos nos estados de São Paulo e Rio de Janeiro e óbitos em Rio Grande do Sul e Rio de Janeiro. No Kernel, verificou-se alta densidade no Sudeste, Sul e Nordeste, principalmente no Rio Grande do Sul, Rio de Janeiro e Santa Catarina, para a taxa de mortalidade. Enquanto isso, no Índice Local de Moran, *clusters* de alto valor estão no Sudeste, Sul e Centro-Oeste, sendo estes também os locais para a taxa de mortalidade. **Conclusão:** os casos se concentraram no estado de São Paulo e Rio de Janeiro, enquanto as taxas de mortalidade atingiram maior densidade no Rio Grande do Sul e Rio de Janeiro. Essas descobertas apontam para a necessidade de estratégias regionais de enfrentamento, como o fortalecimento de campanhas educativas e de prevenção.

Descritores: *HIV. Síndrome da Imunodeficiência Adquirida. Saúde Pública. Estudos Ecológicos. Análise Espacial.*

RESUMEN

Justificación y Objetivos: si bien ha habido avances en el tratamiento antirretroviral y avances en las campañas preventivas, hoy persisten casos y muertes por VIH/SIDA, lo que refleja un grave problema de salud pública. El objetivo de este estudio es realizar un análisis espacial de los casos y muertes por VIH/SIDA en Brasil, 2000-2019. **Métodos:** se trata de un estudio ecológico transversal. Los datos fueron extraídos del Sistema de Información de Enfermedades de Declaración Obligatoria y del Sistema de Información de Mortalidad. Para identificar patrones de distribución espacial y posibles grupos, se crearon mapas Kernel y los Índices Local y Global de Moran de prevalencia y mortalidad en *TerraView* y QGIS. **Resultados:** durante el período de este estudio, hubo 756.586 casos y 232.892 muertes por VIH/SIDA, con las mayores concentraciones de casos en los estados de São Paulo y Río de Janeiro y de muertes en Rio Grande do Sul y Río de Janeiro. En Kernel, hubo alta densidad en el Sudeste, Sur y Nordeste, principalmente en Rio Grande do Sul, Rio de Janeiro y Santa Catarina para la tasa de mortalidad. Mientras tanto, en el Índice Local de Moran, los conglomerados de alto valor se encuentran en el Sudeste, Sur y Centro-Oeste, que también son las ubicaciones de la tasa de mortalidad. **Conclusión:** los casos se concentraron en los estados de São Paulo y Río de Janeiro, mientras que las tasas de mortalidad alcanzaron mayor densidad en Rio Grande do Sul y Río de Janeiro. Estos hallazgos apuntan a la necesidad de estrategias regionales para afrontar la situación, como el fortalecimiento de campañas educativas y de prevención.

Palabras Clave: *VIH. Síndrome de Inmunodeficiencia Adquirida. Salud Pública. Estudios Ecológicos. Análisis Espacial.*

INTRODUCTION

Acquired Immunodeficiency Syndrome (AIDS) is a disease caused by the Human Immunodeficiency Virus type 1 (HIV-1), which affects the immune system, attacking and destroying CD4+ T cells, which can result in serious complications.[1]

AIDS has already affected millions of people worldwide, with 1.3 million cases of infection and 690,000 deaths in 2023. Global estimates indicate that around 39 million people live with HIV worldwide, presenting a serious public health concern.[2] In Brazil, since the beginning of its spread until 2023, 1,124,063 cases of AIDS have been identified.[3]

The pattern of spread and mortality of HIV/AIDS can be instigated by sociodemographic differences, social inequality, health determinants and conditions[4]. Thus, it is known that the social determinants of health can influence the regional distribution of AIDS and the quality and expectancy of life through access to diagnosis, treatment and quality of life of people living with HIV/AIDS.[4] From this perspective, public actions and policies must consider local realities, profile and sociocultural characteristics of communities.[5]

Since the first signs of this HIV-1 pandemic, many actions, such as campaigns to prevent vertical transmission, development of antiretroviral therapies (ART), studies and political decisions, such as the free distribution of medications and the introduction of pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP), have been taken to reverse and advance infected individuals' quality of life.[6] As it is considered a chronic disease, it requires greater attention from the population and healthcare professionals, requiring actions to stop its expansion.[7]

Currently, there is significant ART coverage among underdeveloped countries, accounting for 50% of people treated for the virus[8]. Brazil is considered an exception, as it is one of the few countries that provides free distribution of antiretrovirals[3]. ART has leveraged benefits in reducing AIDS morbidity and mortality and associated comorbidities, providing a better quality of life for people with HIV/AIDS. Moreover, PEP and PrEP are effective developments in the treatment, care and prevention of infection available in the Brazilian Health System (In Portuguese, *Sistema Único de Saúde* - SUS).[9]

HIV-1 causes several harms to the population, such as compromising the human immune system, increasing

vulnerability to opportunistic infections, and facing social stigma. The virus also has a high morbidity and mortality rate, affecting the population's workforce, with direct and indirect impacts that compromise productivity and social and economic well-being as well as overloading healthcare services.[4]

Spatial analysis tools are capable of identifying, delimiting and locating areas at risk for HIV/AIDS transmission and the occurrence of this disease, providing support for decision-making regarding control and reduction of harm to the population at risk.[10]

Given this context, this research is justified by the hypothesis that, although there has been progress in ART and advances in preventive campaigns, cases and deaths persist to this day, reflecting a serious public health concern in Brazil, making it necessary to identify which are the priority areas for greater interventions in relation to HIV/AIDS. This study aimed to carry out a spatial analysis of HIV/AIDS cases and deaths in Brazil from 2000-2019.

METHODS

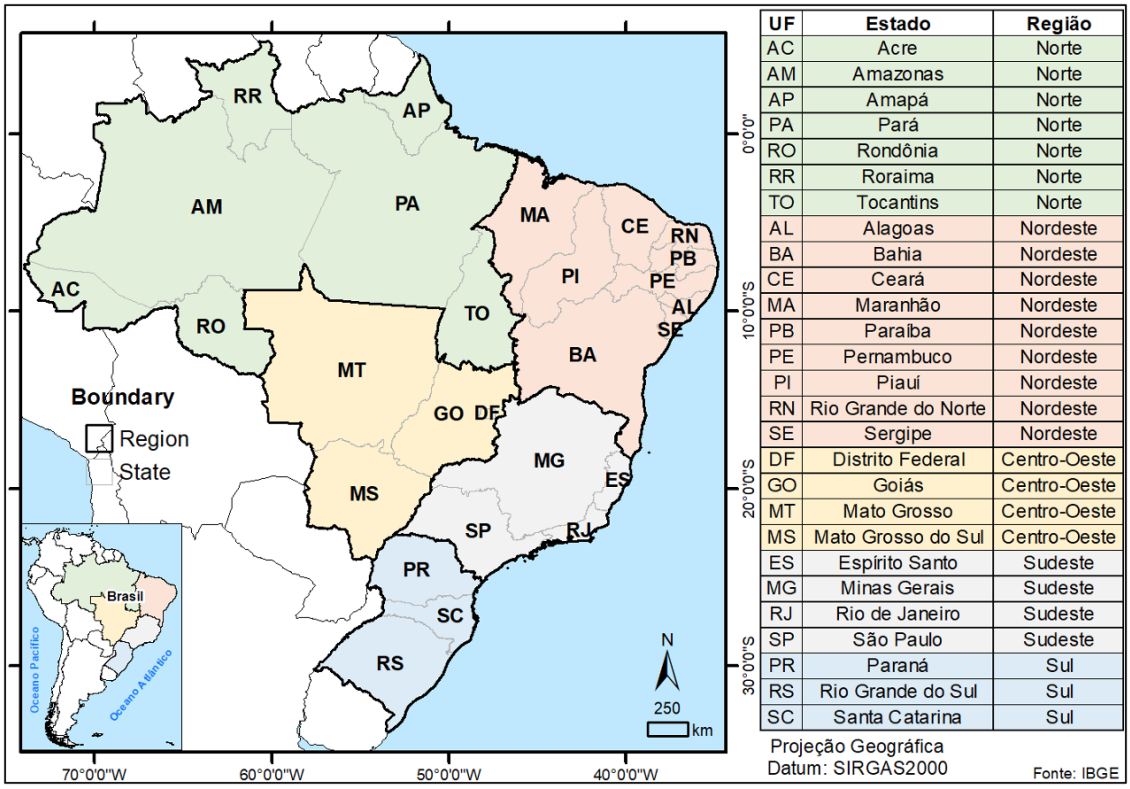
This is an ecological study in Brazil, based on all confirmed cases in the Notifiable Diseases Information System (In Portuguese, *Sistema de Informação de Agravos de Notificação* - SINAN) and deaths from HIV/AIDS registered in the Mortality Information System (In Portuguese, *Sistema de Informação sobre Mortalidade* - SIM), from 2000 to 2019, according to the state. Access was via TabNet, available on the DATASUS platform (https://datasus.saude. gov.br/), accessed on December 10, 2020.

Brazil is located in South America, with a territorial area of 8,516,000 km^2, administratively divided into 5,570 municipalities, 26 states and the Federal District, and five geographic regions (North, Northeast, Southeast, South and Midwest) (Figure 1), with a population of 203,062,512 million inhabitants, a Human Development Index of 0.754 and a Gini of 0.491.[11]

The variables used for confirmed cases were year of diagnosis, region, and state, and for deaths, they were year of registration, region, state, and death by residence. The prevalence and mortality rates were calculated for the total period and by decade. For prevalence, the number of confirmed cases was divided by the population, multiplied by 100,000 inhabitants. Mortality was calculated based on the ratio of the number of deaths to the population, multiplied by 100,000 inhabitants. The data related to the population are based on population estimates for each year carried out by the Brazilian Institute of Geography and Statistics.

For the spatialization of HIV/AIDS epidemiological indicators in Brazil, analyses were performed by geographic region, state and municipality. Maps of total case distribution, Kernel, Local and Global Moran maps were created by grouping points of case prevalence and mortality rate.

Kernel density was used as an alternative for analyzing the behavior of rate density patterns. Adaptive ray was used because it corresponds to a statistical method in which, through the interpolation of point



UF	Estado	Região
AC	Acre	Norte
AM	Amazonas	Norte
AP	Amapá	Norte
PA	Pará	Norte
RO	Rondônia	Norte
RR	Roraima	Norte
TO	Tocantins	Norte
AL	Alagoas	Nordeste
BA	Bahia	Nordeste
CE	Ceará	Nordeste
MA	Maranhão	Nordeste
PB	Paraíba	Nordeste
PE	Pernambuco	Nordeste
PI	Piauí	Nordeste
RN	Rio Grande do Norte	Nordeste
SE	Sergipe	Nordeste
DF	Distrito Federal	Centro-Oeste
GO	Goiás	Centro-Oeste
MT	Mato Grosso	Centro-Oeste
MS	Mato Grosso do Sul	Centro-Oeste
ES	Espírito Santo	Sudeste
MG	Minas Gerais	Sudeste
RJ	Rio de Janeiro	Sudeste
SP	São Paulo	Sudeste
PR	Paraná	Sul
RS	Rio Grande do Sul	Sul
SC	Santa Catarina	Sul

Figure 1. Map of Brazil according to the 26 states, including the Federal District, and the five geographic regions.

data per unit area, a smoothly curved density surface can be modeled, adjusted over each analyzed point with higher surface values at its location, which decrease with increasing distance from the point, obtained through the Silverman equation:[12]

$$\hat{f}(x) = \frac{1}{nh^2} \sum_{i=1}^{n} K\left\{\frac{x - X_i}{h}\right\}$$

Where:
x = coordinate vector of observed point;
n = total points analyzed;
h = bandwidth;
K = Kernel function;
X_i = vector of i-th coordinate of each point existing in the neighborhood of observed point.

In addition to the density study, the investigation of data spatial autocorrelation is proposed. This resource analyzes the degree of dependence between the values observed in the study area, i.e., it estimates how much the value of an attribute in a region is dependent on the values of that same attribute in the neighborhood.[13] To verify spatial autocorrelation, Global and Local Moran's Indices were calculated.

Global Moran's Index is widely used to indicate the existence of spatial autocorrelation in a data set. It is a normalized index in which attribute values are subtracted from their mean and divided by standard deviation, which is based on an initial null hypothesis that there is no spatial dependence. Its values vary within a range of -1 to +1, with the closer to +1, the stronger the spatial dependence, indicating similarity between the attribute value and its surroundings. Values equal to or very close to 0 indicate that there is no spatial autocorrelation and that the aforementioned null hypothesis is true. Negative values are rarely obtained, but when they do occur, they indicate areas with negative autocorrelation.[14,15]

Local Moran's Index was applied to identify areas of confluence of confirmed HIV/AIDS cases, consisting of municipalities that have spatial autocorrelation, allowing the classification of municipalities according to their arrangement in the quadrants of the Moran Scatterplot, with two uniform classes: high with high neighborhood (1st quadrant), for municipalities that have spatial correlation and have high values; low with low neighborhood (2nd quadrant), for municipalities that present spatial correlation and have low values; as well as two other classes for outliers: high with low neighborhood (3rd quadrant), for municipalities that present spatial correlation, but have neighbors with low values; low with high neighborhood (4th quadrant), for municipalities that have spatial correlation, but have neighbors with high values.

The results were validated by applying a significance test using random permutation, in which 999 permutations were performed, with a 95% confidence level. Additionally, the Z score and p-value were determined, both measured based on the statistical significance that indicates whether the visible similarity (clusters of high or low values) or dissimilarity (outliers) is more pronounced than in a random distribution.

A positive and high Z score indicates that the data present clusters with high or low values, relating to the occurrence and size of the uniform classes (1st and 2nd quadrants). Meanwhile, a negative and low Z score indicates a statistically significant spatial data outlier. A p-value < 0.001 indicates that Global Moran's Index is considered significant.

The data from this study were organized in Microsoft Office Excel® 2019 spreadsheets and R version 4.0.2 to produce graphs and tables. The geoprocessing of Moran maps was performed in the free software TerraView, and the map formulation layouts were developed using QGIS 2.18.9. To develop the Kernel maps, the QGIS software was used, which has the heat maps feature, in which the Silverman quartic function was selected.[12] For the distribution and Kernel maps, the classes were stratified by quartile.

The study did not require submission to the Research Ethics Committee, in accordance with section III of Resolution 510/2016 of the Brazilian National Health Council, as the data obtained was secondary and publicly known.[16]

RESULTS

In spatial distribution analysis, of the 756,586 confirmed cases of HIV/AIDS, it is noteworthy that the Southeast region accounted for more than 348,400 (46.0%) of the cases between 2000-2019 (Figure 2A), mainly in the states of São Paulo (181,204 cases), Rio Grande do Sul (South), Bahia (Northeast), Pará (North) and Goiás (Midwest) (Figure 2B) and large extensions of low concentration clusters in the countryside regions of Bahia, Piauí and Tocantins, and in the West of Amazonas and Acre. In the coastal regions, in the South and Southeast, higher occurrences of the medium and high-risk classes are observed (Figure 2C).

When comparing the two decades 2000-2009 and 2010-2019, an increase was noted in areas of medium and high density of prevalence of cases in the Southeast and Northeast regions in the second decade. Among the top five states in the country, those that showed the most cases were São Paulo (23.0%), Rio de Janeiro (12.9%), Rio Grande do Sul (10.6%), Minas Gerais (7.3%) and Santa Catarina (5.4%). Meanwhile, the states of Acre (0.15%), Amapá (0.3%), Roraima (0.3%), Tocantins (0.3%) and Sergipe (0.6%) showed a lower frequency (Figure 3).

Concerning deaths, 232,892 deaths were recorded, with the highest mortality rates occurring in Rio Grande do Sul (12.30/100,000 inhab.) and Rio de Janeiro (10.50/100,000 inhab.), regardless of the period (Figure 4).

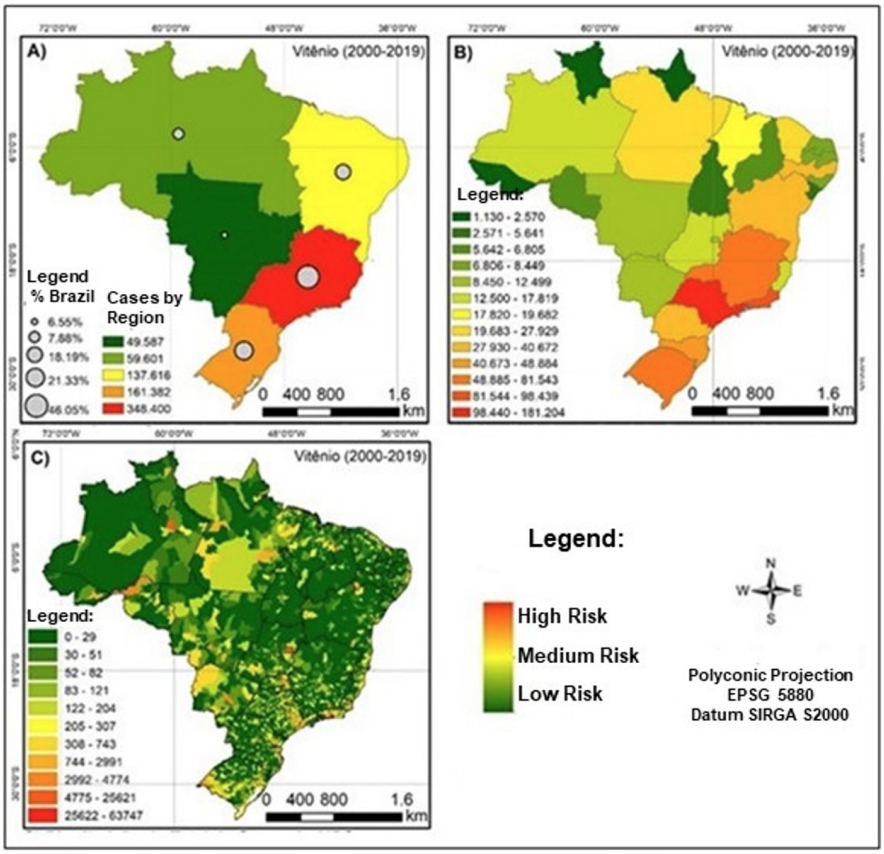


Figure 2. Map of the distribution of HIV/AIDS cases in regions (A), states (B) and municipalities (C) of Brazil between 2000 and 2019.

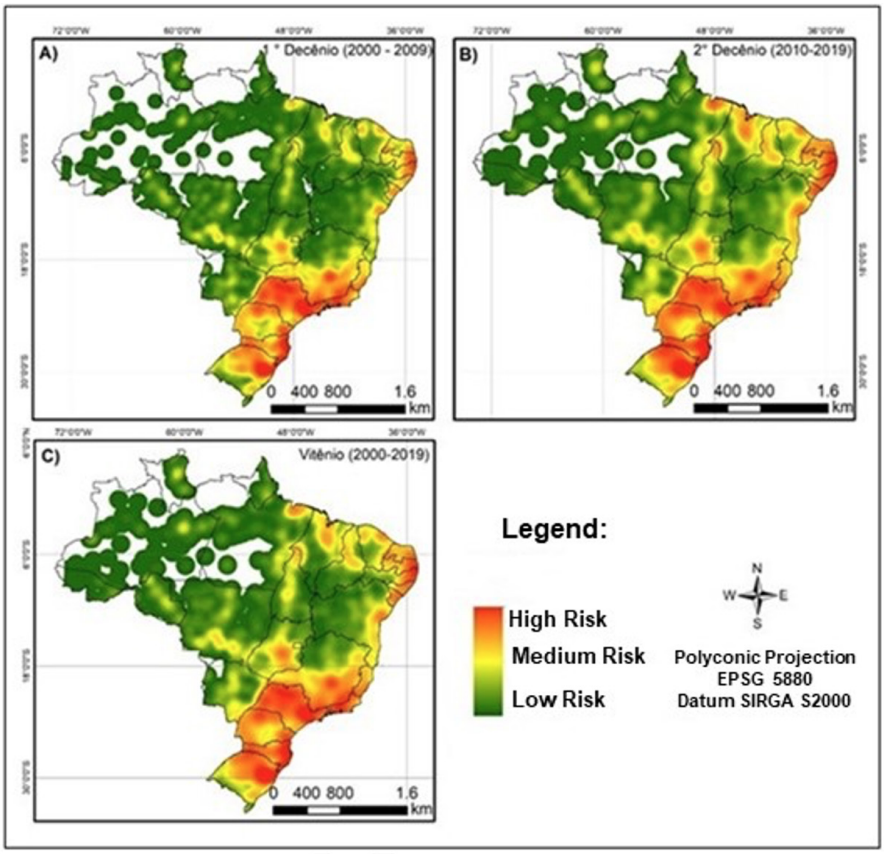


Figure 3. Kernel map of the prevalence rate of HIV/AIDS cases according to the first decade (2000-2009) (A), second decade (2010-2019) (B) and total period (2000-2019) (C) in Brazilian municipalities between 2000 and 2019.

It was observed that, in A and B, the high-value clusters extend over the Southeast, South and Midwest. Meanwhile, practically the entire Northeast is classified as a low-value cluster. The North region presented three low-value clusters in A, while in B there were low-value classes. Both present occasional occurrences of outliers, and it is important to highlight a small high-value cluster in Belém do Pará for both images. Global Moran's Index reflects the average positive spatial autocorrelation (p-value <0.001) (Figure 5).

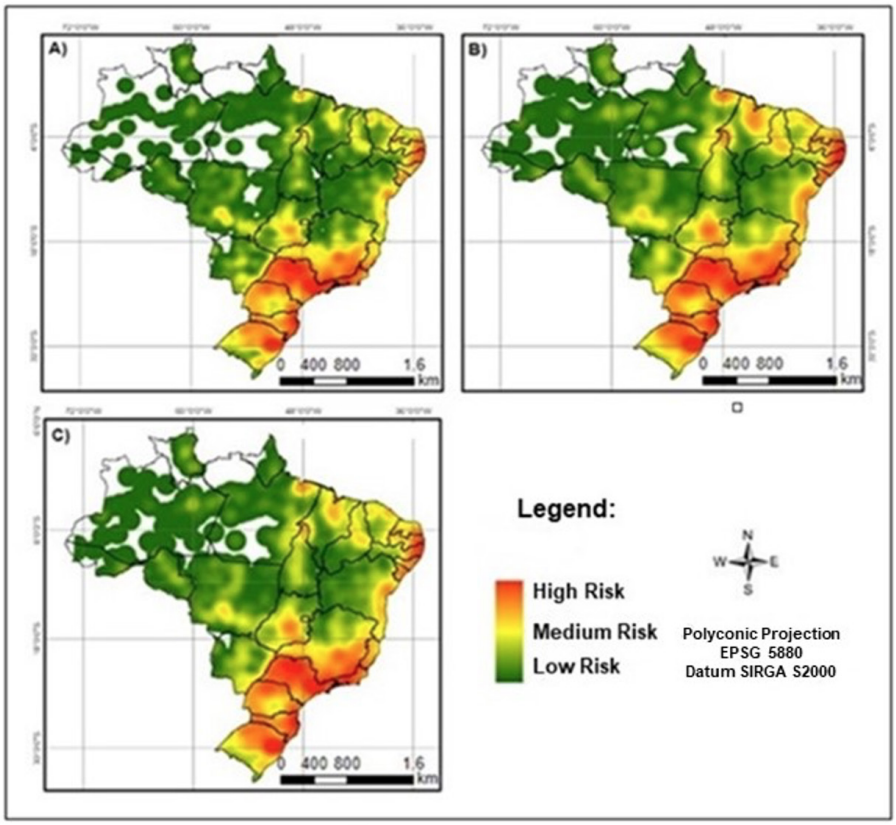


Figure 4. Kernel maps of the HIV/AIDS mortality rate according to the first decade (2000-2009) (A) second decade (2010-2019) (B) and total period (2000-2019) (C) in Brazilian municipalities between 2000 and 2019.

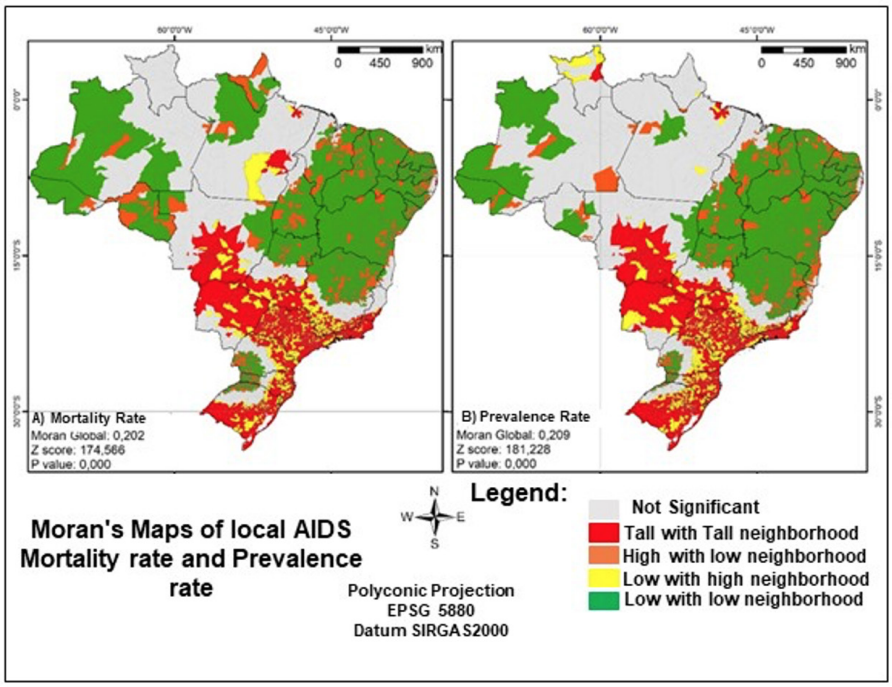


Figure 5. Moran Local Map of HIV/AIDS mortality rates (A) and HIV/AIDS prevalence rate (B) in Brazil between 2000 and 2019.

DISCUSSION

The distribution of HIV/AIDS in Brazil found in the study is not homogeneous across the Brazilian territory. The highest concentration of cases and deaths occurred in the Southeast and South geographic regions, which have populous states, large urban centers and municipalities with greater socioeconomic and demographic flow.[17] The geographical differences identified in this study showed a greater concentration of confirmed cases in the states of São Paulo and Rio de Janeiro, and deaths in Rio Grande do Sul, Rio de Janeiro and Santa Catarina prevailed.

In spatial analysis of Figure 2A, the Southeast region had the highest concentration of cases, being the region of greatest concern regarding HIV infection in the country. This is probably related to the high prevalence, taking into account population density. The states in the Southeast region are the most populous, with a large concentration of people.[17] Furthermore, the literature shows that the initial emergence of the spread of HIV/AIDS in Brazil occurred primarily in urban areas of the Rio de Janeiro-São Paulo axis, states located in this region, gradually expanding to other regions of the country. Initially, it reached the large metropolises and, later, reached the more remote areas with smaller cities. Therefore, it is plausible to suggest that the results of this study can be partially attributed to the historical trajectory of the spread of the epidemic in the country.[18]

A study carried out on HIV/AIDS cases in southeastern Brazil identified that their concentrations are related to the sociodemographic and socioeconomic flow of territories and that geographical differences influence the increasing risk in the distribution of the disease in space. [18] The cases are concentrated in socioeconomically vulnerable population groups, marked by social inequalities.[18] In Figure 2C, it was identified that the areas where large extensions of the low-density classes of the states occurred are marked by low population density and municipalities of large territorial extension. While in the coastal regions, in the South and Southeast, there are greater occurrences of medium and high-density classes, due to the high population density, but little apparent because of the small size of most municipalities in the region. In the Kernel maps of the prevalence rate, it is possible to better distinguish the influence of these municipalities.

In the map in Figure 3A, B and C, a relevant prevalence was observed in the Southeast region. This may be related to the economy, culture and social factors that influence a higher prevalence of the infection, given that people with low socioeconomic conditions, digitally excluded populations, migrants, injecting drug users, sexual partnerships with high-risk individuals, among other social vulnerabilities, are some characteristics for the tendency of this disease.[19] Furthermore, this scenario is worse in regions with less digital infrastructure, where educational campaigns do not effectively reach the most vulnerable communities.[19,20]

Meanwhile, the North region presented a low density of HIV/AIDS prevalence, which may be related to the fact that this region has a low population index and does not have metropolitan centers with characteristics conducive to dissemination.[20]

The finding regarding the increase in areas of medium and high concentration of the prevalence of HIV/AIDS cases, in spatial analysis, between 2010-2019, may be related to the fact that there is still no wider testing for the disease and the lack of adherence to immediate treatment in the event of a positive diagnosis, as these factors are essential for reducing cases and deaths.[19]

In mortality coefficient analysis, the South stood out more, and in a study on deaths from HIV/AIDS in Brazil, between 2000 and 2015, a worrying scenario was identified throughout the country[21]. In a study on the trend of mortality from HIV/AIDS and sociodemographic characteristics, in the states of Porto Alegre and Rio Grande do Sul, an increase in the number of deaths in women, of mixed race/color and older ages was identified. [22] This may be related to lack of adherence to ART, cultural and social factors, and mitigation strategies.[22] In contrast, mortality data from this infection showed a decrease in the total period in the current study.

The Plan of Action for the prevention and control of HIV and sexually transmitted infections 2016-2021 aims to eradicate the epidemic in the Americas by 2023, but it failed to achieve this goal. Despite advances, such as the expansion of ART and reduction in infections, the challenges of insufficient testing and unequal access have limited the achievement of this goal. However, in the Latin American region, of which Brazil is a part, mortality decreased from 41,000 to 37,000 between 2010 and 2019, evidencing a significant decrease.[23]

However, in a study on the competing risks model for analyzing mortality from HIV/AIDS in Brazil,[5] it was pointed out that, despite diagnosis and treatment being made available by the SUS and a reduction in the number of deaths, as found in this present study, the major problem in the country is the challenge of controlling the disease incidence. This may be related to treatment abandonment, multiple sexual partners without condoms, injectable drug use and late diagnosis.[24] Therefore, promoting testing and early diagnosis, implementing public policies for integration with the service and intensifying prevention and harm reduction are strategies to reduce incidence.

In the Kernel map analysis in Figure 4, it was identified that Rio Grande do Sul has the highest density of deaths. This state has late access to HIV/AIDS diagnosis, a long start of treatment for the virus infection and a medium percentage of individuals who abandon treatment, in addition to existing inequalities in access to treatment services for the disease.[9]

In a study conducted in three specialized HIV/AIDS services in Porto Alegre, in the state of Rio Grande do Sul, it was found that most men know their HIV status due to other diseases, such as tuberculosis, chest pain, donating blood or after numerous visits to healthcare services. However, spontaneous testing only occurs after the perception of some possible risk of infection, symptoms or guidance from someone,[24] which can lead to a delay in

diagnosing the disease and reflect in the increase in the number of deaths in the state.

Comparing the Kernel maps of mortality and prevalence rates, a smaller spread of the medium density class was observed. Furthermore, the regions classified as high density appear on the prevalence rate map with a more concentrated focus, while a smoother spatialization is observed on the mortality rate maps. This difference is due to the variation in the values of confirmed cases of HIV/AIDS, which is much higher than the variation in the occurrence of deaths due to HIV/AIDS.

In the analysis using Local Moran's Index on the map in Figure 5A and B, clusters were found in the Southeast, South and Midwest regions. The presence of HIV/AIDS in some regions may be related to the occurrence of specific factors, such as patterns of sexual relations, low condom use, socioeconomic conditions and neglect of healthcare in limited access to healthcare services, regular testing infrastructure.[17] Thus, as they are regions with large cities with high population density, they have greater risks for the disease,[5] while, in the Northeast and North regions, the clusters presented low values, and this may be related to the fact that the classification of many diseases is affected by underreporting, an issue frequently associated with the Northeast region.[25] However, according to literature, the largest increases have resulted in ignorance of the positive result and late access to treatment, resulting in death.[21]

In the different spatial analyses, the Kernel analysis showed the concentration of prevalence in the Southeast, South and Midwest, and Moran's Index had high-value clusters in these regions. Furthermore, there was a low risk of contamination and deaths in the Northeast and Midwest in both analyses. Furthermore, it is inferred that, in locations with more cases, there is a high risk of death from opportunistic diseases due to inadequate adherence to ART, late diagnosis and socioeconomic and structural factors.[22]

This current study has limitations, as it is based on secondary data that may be underreported, which may not demonstrate an accurate analysis of reality. To this end, analyses of duplications, inconsistencies and incompleteness in database were carried out, observing the variables analyzed.

Finally, it can be concluded that, in this study, it was noted that the Southeast region presented the highest cases and deaths, followed by the South, representing the regions with the highest densities, with the highest concentrations of cases in the states of São Paulo (Southeast region) and deaths in Rio Grande do Sul (South region). This is a public health concern that requires greater investment for the development of HIV science, making it relevant to carry out its monitoring, discussions and continuous actions in regions with the highest risks to achieve disease control with comprehensive, equitable and universal care.

Furthermore, it is important to conduct future studies that explore the determining factors of observed regional inequalities, including qualitative and quantitative analyses on the social determinants of health and the impact of local interventions. Furthermore, it is recommended to continuously monitor the epidemic and implement innovative approaches to predict trends and identify critical areas, aiming to achieve disease control.

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AUTHORS' CONTRIBUTIONS

Isadora Sabrina Ferreira dos Santos contributed to project administration, literature research, formal analysis, conceptualization, methodology, data curation, statistics, writing (first draft, review and editing), investigation, resources, software, supervision, validation, conclusions. **Laís Eduarda Silva de Arruda** contributed to writing (review and editing), interpretation of results, conclusions, validation and visualization. **José Thiago de Lima Silva** contributed to project administration, methodology, interpretation of results and review. **Guilherme Lira** contributed to data curation, software, interpretation of results, and review. **Emília Carolle Azevedo de Oliveira** contributed to project administration, literature search, formal analysis, writing (review and editing), investigation, methodology, resources, supervision, validation, and conclusions.

All authors have approved the final version of the manuscript and are responsible for all aspects of it, including ensuring its accuracy and integrity.

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ORIGINAL ARTICLE

Knowledge and adherence to preventive measures for ventilator-associated pneumonia during the COVID-19 pandemic

Conhecimento e adesão às medidas preventivas da pneumonia associada à ventilação mecânica na pandemia de COVID-19

Conocimiento y adherencia a las medidas preventivas de la neumonía asociada a ventilador en la pandemia de COVID-19

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Corresponding Author:
Hélio Galdino Júnior
helio_junior@ufg.br

Address: Rua 1, Chácaras Alto da Glória, Goiânia, Goiás, Brasil.

Ana Clara Alves Campos[1];
Jessica de Oliveira Montebello[1];
George Oliveira Silva[1];
Hélio Galdino Júnior[1];

[1] *Universidade Federal de Goiás, Goiânia, GO, Brasil.*

ABSTRACT

Background and Objectives: adherence to measures to prevent mechanical ventilation-associated pneumonia (VAP) significantly reduces this hospital infection, and knowledge of the measures is essential to ensure adherence. COVID-19 has increased the demand for intensive care and increases the risks and severity of VAP. Thus, the objective was to assess the knowledge referred to about the VAP prevention bundle and its associated factors and multidisciplinary team professionals' perspective about adherence during the COVID-19 pandemic. **Methods:** this is a cross-sectional study, carried out from December 2020 to July 2021, with professionals from the Intensive Care Unit of a university hospital. Bivariate and multivariate analyzes were performed to assess factors associated with professionals' knowledge. **Results:** of the 61 professionals interviewed, 85.2% were nursing professionals and 14.7% were physical therapists. Physical therapists obtained a higher percentage of correct answers in relation to the VAP prevention bundle items. Nursing professionals have little knowledge about the elements that make up the bundle, highlighting the need for training throughout the entire process of training and professional performance. Lack of training was the main difficulty reported (14.75%). Age was a factor associated with knowledge of the bundle (p=0.017). **Conclusion:** there is a lack of knowledge and adherence to the VAP prevention bundle among nursing professionals. However, these professionals demonstrated a willingness to receive training to improve bundle adherence rates and current good VAP prevention practices.

Keywords: *Pneumonia, Ventilator-Associated. Intensive Care Units. Pandemics. Infection Control. COVID-19.*

RESUMO

Justificativa e Objetivos: a COVID-19 aumentou a demanda pela terapia intensiva e intensificou a necessidade de ventilação mecânica e a gravidade da pneumonia associada à ventilação mecânica (PAV). A adoção de medidas

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preventivas da PAV no contexto da pandemia tem grande impacto para salvar vidas. Assim, objetivou-se avaliar o conhecimento referido sobre o *bundle* de prevenção da PAV e seus fatores associados e a percepção dos profissionais da equipe multiprofissional sobre a adesão em vigência da pandemia de COVID-19. **Métodos:** trata-se de estudo transversal, realizado no período de dezembro de 2020 a julho de 2021, com profissionais da Unidade de Terapia Intensiva de hospital universitário. Foram realizadas análises bivariadas e multivariadas para avaliar os fatores associados ao conhecimento dos profissionais. **Resultados:** dos 61 profissionais entrevistados, 85,25% eram profissionais de enfermagem e 14,75% eram fisioterapeutas. Os fisioterapeutas obtiveram maior porcentagem de acertos em relação aos itens do *bundle* de prevenção da PAV. Os profissionais de enfermagem possuem pouco conhecimento sobre os elementos que compõem o *bundle*, remetendo à necessidade de capacitação ao longo de todo o processo de formação e atuação profissional. Falta de treinamento foi a principal dificuldade relatada (14,75%). A idade foi um fator associado ao conhecimento do *bundle* (p=0,017). **Conclusão:** há deficiência no conhecimento e na adesão ao *bundle* de prevenção de PAV entre os profissionais de enfermagem. No entanto, esses profissionais demonstraram disposição em receber capacitação para melhoria das taxas de adesão ao *bundle* e das boas práticas de prevenção da PAV vigentes.

Descritores: *Pneumonia Associada à Ventilação Mecânica. Unidades de Terapia Intensiva. Pandemias. Controle de Infecções. COVID-19.*

RESUMEN

Justificación y Objetivos: el cumplimiento de las medidas para prevenir la neumonía asociada a la ventilación mecánica (NAV) reduce significativamente esta infección hospitalaria, y el conocimiento de las medidas es fundamental para garantizar el cumplimiento. COVID-19 ha aumentado la demanda de cuidados intensivos y aumenta los riesgos y la gravedad de la NAV. Así, el objetivo fue evaluar los conocimientos referidos sobre el paquete de prevención de NAV y sus factores asociados y la percepción de los profesionales del equipo multidisciplinario sobre la adherencia durante la pandemia de COVID-19. **Métodos**: se trata de un estudio transversal, realizado de diciembre de 2020 a julio de 2021, con profesionales de la Unidad de Cuidados Intensivos de un hospital universitario. Se realizaron análisis bivariados y multivariados para evaluar los factores asociados al conocimiento de los profesionales. **Resultados**: de los 61 profesionales entrevistados, el 85,25% eran profesionales de enfermería y el 14,75% eran fisioterapeutas. Los fisioterapeutas obtuvieron un mayor porcentaje de respuestas correctas en relación con los ítems del paquete de prevención de NAV. Los profesionales de enfermería tienen poco conocimiento sobre los elementos que componen el paquete, destacándose la necesidad de capacitación durante todo el proceso de formación y desempeño profesional. La falta de formación fue la principal dificultad reportada (14,75%). La edad fue un factor asociado al conocimiento del paquete (p=0,017). **Conclusión**: existe falta de conocimiento y adherencia al paquete de prevención de NAV entre los profesionales de enfermería. Sin embargo, estos profesionales demostraron voluntad de recibir capacitación para mejorar las tasas de cumplimiento del paquete y las buenas prácticas actuales de prevención de NAV.

Palabras Clave: *Neumonía Asociada al Ventilador. Unidades de Cuidados Intensivos. Pandemias. Control de Infecciones. COVID-19.*

INTRODUCTION

The clinical picture of patients with COVID-19 can range from mild flu-like symptoms to more severe conditions, with systemic manifestations.[1] One of the most frequent complications of severe COVID-19 is acute respiratory distress syndrome (ARDS), causing diffuse alveolar damage, pulmonary capillary thrombi, and endothelial dysfunction, culminating in lung collapse and respiratory failure. This syndrome is the main indication for invasive mechanical ventilation (IMV) in COVID-19.[2]

When subjected to IMV for more than 48 hours, patients are at risk of acquiring ventilator-associated pneumonia (VAP), which occurs when there is contamination of the lungs by exogenous or endogenous bacteria.[3] The occurrence of VAP prolongs the time of ventilator use, increases the length of hospital stay and hospitalization costs, and can contribute to a higher risk of death.[3] Therefore, preventive measures for VAP, offered through a bundle, are essential for the care of critically ill patients with COVID-19 on mechanical ventilation.

The VAP prevention bundle is defined as a set of evidence-based interventions that, when implemented in combination, reduce the risk of VAP.[4] The implementation of the VAP prevention bundle has resulted in a significant reduction in VAP incidence worldwide. In a hospital in Turkey, the VAP rate decreased from 15.91 per 1,000 ventilator days to 8.50 per 1,000 ventilator days.[5] In a hospital in Taiwan, VAP incidence density decreased significantly from 3.3 to 1.4 cases per 1,000 ventilator days after the bundle implementation.[6]

Likewise in Brazil, studies have shown that the bundle implementation reduces the number of VAP cases, mortality and hospital costs, improving the quality of care for patients in intensive care.[7-8]

The increase in new cases of severe pneumonia caused by COVID-19 has led to overcrowding and pressure

in Intensive Care Units (ICUs), resulting in a high rate of mechanical ventilation use. Moreover, it has changed the way these units operate, requiring new isolation spaces, new facilities and urgent hiring to meet this demand.[9]

The increased need for IMV leads to an increased risk of VAP, which, for patients with COVID-19 and ARDS, increases the severity of patients' condition and the chance of shock, septicemia, and death.[10] Therefore, the need to apply the VAP prevention bundle becomes even more expressive to reduce complications and promote patient recovery.

Thus, during the COVID-19 pandemic, in which ICU utilization rates reached 100% of their capacity, it is important to investigate the healthcare professionals' knowledge about the VAP prevention bundle and their adherence in this context. Identifying barriers to adherence can help establish measures to strengthen the application of these care measures, thus helping to reduce VAP rates in ICUs. Thus, the objective of this study was to assess the knowledge reported on the VAP prevention bundle and its associated factors and the perception of nursing and physical therapy team professionals regarding adherence, during the COVID-19 pandemic, in a hospital in Goiânia, Goiás.

METHODS

Study design, period and site

This is a cross-sectional study conducted in an ICU specifically for the care of patients with COVID-19 in a large hospital in Goiânia, Goiás, Brazil, from January to December 2021.

Sample and eligibility criteria

The study population consisted of professionals directly involved in the implementation of the actions that make up the VAP prevention bundle, such as nurses, nursing technicians and physical therapists. The sampling process for this study was by convenience, in which all ICU professionals were invited to participate, following the following inclusion criteria: having worked for more than five months in the unit and being part of the nursing or physical therapy team. Participants who responded less than 50% of the instrument were excluded. Of the 80 professionals eligible for the study, 71 agreed to participate; of these, ten were excluded due to incomplete completion of the instrument. Thus, the sample consisted of 61 professionals, representing 76.2% of the intended population.

Data collection

Data were collected from January to August 2021. Professionals were contacted personally at their work unit and invited to participate in the study. Those who accepted agreed to participate with the data collection team, depending on their availability to respond to the instrument. Data were collected in a room attached to the unit, where the professional responded to the instrument and, at the end, returned it to the researcher.

The data collection instrument was structured in three parts, namely: 1. Sociodemographic data; 2. Professional participation in continuing education activities addressing VAP prevention measures and their perception of adherence to the bundle during the pandemic (dichotomous closed-ended questions); 3. Open-ended question: "What interventions make up the VAP prevention bundle?". The instrument was developed by the research team, based on the Brazilian National Health Regulatory Agency (In Portuguese, *Agência Nacional de Vigilância Sanitária* - ANVISA) Healthcare-Associated Infection Prevention Measures.[11-12] It was submitted for analysis by three judges with PhDs in nursing and working in healthcare-associated infection control (HAI) services. After adjustments, the instrument was validated by a pilot test in the ICU of another institution.

Study variables

The dependent variable was knowledge of elements that make up the VAP prevention bundle (oral hygiene, elevated head of the bed, checking cuff pressure, possibility of extubation, daily awakening/reduction of sedation and adequate ventilation system maintenance). For each participant, the number of items that make up the bundle was counted, categorized as: knows up to three elements of the bundle and knows more than three elements of the bundle. Independent variables were divided into sociodemographic and professional data, and information related to participation in continuing education activities, detailed in Table 1.

Data analysis

The data were analyzed using the statistical program R version 4.3.1. Descriptive analyses were performed with presentation of qualitative data in the form of absolute and relative frequencies and quantitative data in the form of median and interquartile range. The relative frequencies with respective confidence intervals on the incentive to adhere to the prevention bundle and knowledge of each element were presented in the form of a bar graph. The chi-square test for trend was used to compare the encouragement to adhere to the bundle before the pandemic with the period during the pandemic. Logistic regression models were used to perform bivariate and multivariate analyses of factors associated with knowledge of elements of the VAP prevention bundle, from which unadjusted and adjusted Odds Ratios (OR) were obtained.

Variables that presented $p<0.2$ were included in the multivariate model, so the stepwise strategy was established as the input method for these variables into the model, in which they are included in the model so that the adjustment identifies whether it is feasible to include or remove them, with the model starting without any variables until a model with a better fit is identified. As a criterion for defining the model's fit, we established the Akaike Information Criterion (AIC). Thus, the final model included only the variables that fit best. Variables that presented a p-value <0.05 were considered statistically significant.

The study protocol was submitted to and approved by the Research Ethics Committee of the *Hospital*

Table 1. Characterization of predictor variables of professionals' knowledge about the elements that make up the ventilator-associated pneumonia prevention bundle. Goiânia, GO, Brazil, 2021.

Type	Variables / Categorization	Type of variable
Sociodemographic and professional data	**Sex**	Qualitative
	Female	
	Male	
	Age	
	Profession	Qualitative
	Nursing technicians	
	Nurses	
	Physical therapists	
	Training period	Quantitative
	In years	
	Job tenure in the unit	Quantitative
	In months	
	Other employment relationship	Qualitative
	Yes	
	No	Qualitative
Participation in continuing education activities	**Participation in training on the bundle (in the unit)**	
	Yes	
	No	Qualitative
	Participation in training on the bundle (in the other link)	
	Yes	
	No	Qualitative
	Felt encouraged to apply the bundle (before the pandemic)	
	Yes	
	No	Qualitative
	Felt encouraged to apply the bundle (during the pandemic)	
	Yes	
	No	Qualitative
	Believe that the pandemic influenced the bundle implementation	
	Yes	
	No	Qualitative
	Believe that the pandemic influenced the bundle completion	
	Yes	
	No	

das Clínicas at the *Universidade Federal de Goiás* (CAAE 41340620.3.0000.5078, approval protocol 4,499,285 on 01/14/2021), and followed all ethical recommendations of Resolution 466/2012.

RESULTS

Sixty-one professionals from an ICU dedicated to treating patients with COVID-19 participated in the study. Table 2 presents participant sociodemographic and professional profile. The aim was to determine whether the professionals received training on the VAP prevention bundle before and during the pandemic. Before the pandemic, 37.4% of professionals reported having received training on the VAP prevention bundle, and 26.2% of professionals interviewed reported training on the VAP prevention bundle in the study unit during the pandemic period. There was an increase in the incentive to adhere to the VAP prevention bundle during the pandemic period in relation to the pre-pandemic period ($p<0.001$) (Figure 1).

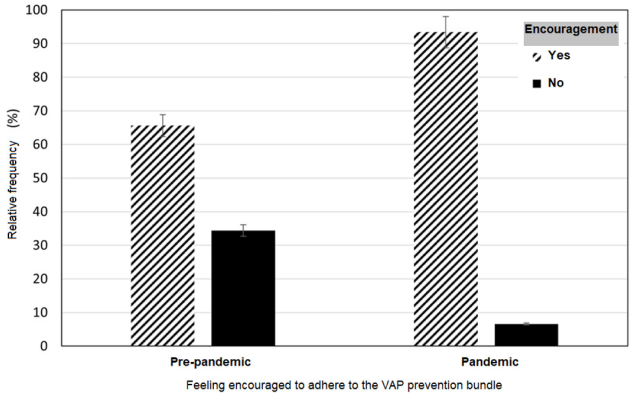
Concerning knowledge of items that make up the VAP prevention bundle, oral hygiene was the most reported item (65.7%), followed by elevating the head of the bed (45.9%) and checking cuff pressure (19.6%). When analyzed by professional category, physical therapists obtained a higher percentage of correct answers. In this professional category, all elements of the bundle were mentioned, although some elements appeared more frequently than others. No member of the nursing team listed all the elements that make up the VAP prevention bundle. Nurses mentioned up to four (66.7%) of the six recommended practices, and nursing technicians mentioned a maximum of three (50%). Oral hygiene was the most frequently reported intervention in the bundle among nursing professionals, followed by elevated headboard and cuff pressure check, which was mentioned by 47.6% and 14.3% of nurses, respectively, and 35.2% and 5.5% of nursing technicians, respectively. Daily awakening from sedation was reported only by physical therapists.

In relation to factors associated with knowledge of the bundle, bivariate analyses showed an association wi-

Table 2. Sociodemographic characteristics and adherence to the ventilator-associated pneumonia prevention bundle among professionals in an Intensive Care Unit for COVID-19 patients participating in the study. Goiânia, GO, Brazil, 2021.

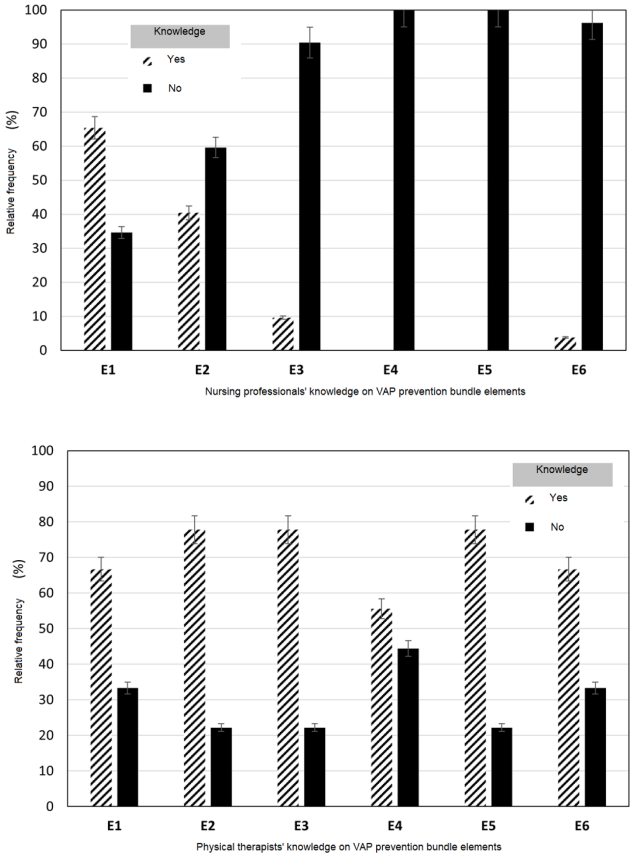
Variables	N(%)
Sex	
Female	52 (85.2%)
Male	9 (14.8%)
Profession	
Nursing technicians	31 (50.8%)
Nurses	21 (34.4%)
Physical therapists	9 (14.8%)
Other employment relationship	
Yes	48 (78.7%)
No	13 (21.3%)
Participation in training on the bundle (in the unit)	
Yes	19 (31.1%)
No	42 (68.9%)
Participation in training on the bundle (in the other link)	
Yes	14 (22.9%)
No	47 (77.1%)
Felt encouraged to apply the bundle (before the pandemic)	
Yes	40 (65.6%)
No	21 (34.4%)
Felt encouraged to apply the bundle (during the pandemic)	
Yes	57 (93.4%)
No	4 (6.6%)
Believe that the pandemic influenced the bundle implementation	
Yes	40 (65.4%)
No	21 (34.4%)
Believe that the pandemic influenced the bundle completion	
Yes	39 (65%)
No	21(35%)
Age (years) [median (IQR*)]	50 (47 – 54)
Time since graduation [median (IQR*)]	19 (14 – 25)
Job tenure in the unit [median (IQR*)]	12 (6 – 15)

*Note: *IQR = interquartile range.*



*Note: *Chi-square test for trend.*

Figure 1. The COVID-19 pandemic increased the frequency of professionals who felt encouraged to adhere to the ventilator-associated pneumonia prevention bundle. Goiânia, GO, Brazil, 2020-2021.



Note: A: nursing professionals; B: physical therapists; E1: oral hygiene; E2: elevated head of bed; E3: checking cuff pressure; E4: possibility of extubation; E5: daily awakening/ reduction of sedation; E6: adequate ventilation system maintenance.

Figure 2. Knowledge of ventilator-associated pneumonia prevention bundle elements among Intensive Care Unit professionals during the COVID-19 pandemic. Goiânia, GO, Brazil, 2021.

th age, participation in training on bundle V in the other employment relationship, feeling encouraged to apply the bundle and believing that the pandemic influenced the bundle implementation. In the multivariate analysis, only age remained statistically significant, showing that the younger the age, the greater the knowledge about the bundle (OR: 0.83; 95% CI: 0.71 – 0.96; p=0.017) (Table 3).

DISCUSSION

VAP is one of the most common HAIs in ICUs, and can worsen patients' clinical conditions and increase their chances of death. However, correctly implemented prevention measures can reduce the incidence of this infection and its impacts.[6]

The COVID-19 pandemic, in which the management of the severe form of the disease requires ventilatory support in the ICU, has caused overcrowding, increased rates of mechanical ventilation use and contributed to the increased risk of VAP incidence.[13] Therefore, it is essential to diagnose the knowledge and practice of professionals

Table 3. Factors related to knowledge of ventilator-associated pneumonia prevention bundle elements among Intensive Care Unit professionals during the COVID-19 pandemic. Goiânia, GO, Brazil, 2020-2021.

Variables	Knowledge [n (%)] > three elements (n=6)	Up to three elements (n=55)	Unadjusted OR* (95% CI)	p-value	Adjusted OR* (95% CI)	β†	p-value‡
Sex							
Female	5 (9.6)	47 (90.4)	0.85 (0.08; 8.27)	0.889			
Male	1 (11.1)	8 (88.9)	1				
Age [median (IQR§)]	36.5 (33.2; 43.5)	51.0 (49.0; 54.0)	0.80 (0.69; 0.93)	0.003	0.83 (0.71; 0.96)	-0.185	0,017
Profession							
Nurse	1 (4.8)	20 (95.2)	-	0.998			
Physical therapist	5 (55.6)	4 (44.4)	-	0.997			
Nursing technician	0 (0.0)	31 (100.0)	1				
Another employment relationship							
Yes	6 (12.5)	42 (87.5)	-	0.995			
No	0 (0.0)	13 (100.0)	1				
Time since training [median (IQR§)]	15.0 (10.7; 17.7)	6.8 (14.0; 25.0)	0.84 (0.71; 1.00)	0.052			
Job tenure in the unit [median (IQR§)]	7.5 (6.2; 13.2)	12.0 (6.0; 15.0)	0.94 (0.79; 1.12)	0.531			
Participation in training on the bundle (in the unit) [during the pandemic]							
Yes	1 (5.26)	18 (94.7)	0.41 (0.04; 3.78)	0.433			
No	5 (11.9)	37 (88.1)	1				
Participation in training on the bundle (in the other link)							
Yes	4 (28.6)	10 (71.4)	8.99 (1.44; 56.12)	0.018			
No	4 (4.3)	45 (95.7)	1				
Feel encouraged to apply the bundle							
Yes	4 (7.0)	53 (93.0)	0.07 (0.01; 0.68)	0.021			
No	2 (50.0)	2 (50.0)	1				
Believe that the pandemic influenced the bundle implementation							
Yes	1 (2.5)	39 (97.5)	0.08 (0.01; 0.75)	0.027	0.17 (0.01; 1.89)	-1.76	0,149
No	5 (23.8)	16 (76.2)	1		1		
Believe that the pandemic influenced the bundle completion							
Yes	2 (5.1)	37 (94.9)	0.23 (0.04; 1.37)	0.107			
No	4 (19.1)	17 (80.9)	1				

*Note: *OR = Odds Ratio; † β = model coefficients; ‡p-value = significance level; §IQR = interquartile range; model fit parameter: AIC=53.89.*

in the application of VAP prevention measures which, if well targeted, can significantly reduce this complication.[6,14]

In the ICU assessed in this study, the physical therapy team was directly responsible for registering the bundle, but most studies regarding adherence to this tool, in different parts of the world, are aimed at the nursing team,[15-16] which highlights the leading role of this professional team in the application of VAP preventive measures. Thus, our study innovated by including physical therapists as participants, in addition to nursing professionals, due to their institutional responsibility in the bundle application and registration and their recognized interprofessional performance in VAP prevention.[17]

Only 26% of professionals reported having received training on the VAP prevention bundle at the institution. Since VAP is one of the main adverse events for critical care patients, it would be essential for workers in this sector to be periodically updated. The number of professionals who received training at other institutions was also low, showing that not only at the study institution, but also in other services, investment in continuing education for VAP prevention is insufficient.

It has been shown that patients with COVID-19 are at higher risk of developing VAP[21] and that VAP in patients with COVID-19 was associated with greater complications, such as shock (71% vs. 48%, p = 0.009), ICU death (52% vs. 30%, p = 0.011), and bacteremia (26% vs. 13%, p = 0.038), than patients who develop VAP without COVID-19.[10] These findings make the application of VAP prevention bundles essential in the context of the COVID-19 pandemic.

Considering the importance of applying VAP prevention bundles, some factors can be suggested for the low number of professionals who reported training in VAP prevention, such as a shortage of professionals, due to the expansion in the number of beds, and high turnover, due to the replacement of infected professionals, generating emergency hiring of professionals with little

experience, in addition to a large number of new management and assistance demands related to preventive measures against infection in the unit.

Before the pandemic, only 65% of survey participants reported feeling encouraged to apply the bundle, a worrying fact, since this infection is preventable and has harmful consequences for patients and healthcare services, increasing their costs.[8-11]

It is noteworthy that, during the pandemic, most professionals felt more encouraged to apply the VAP prevention bundle (93%), compared to the period before the pandemic ($p<0.001$). It is important to highlight that the variable feeling encouraged to apply the bundle was a self-report by participants and does not reflect real adherence, which was not the target of this investigation. Despite this, low knowledge among nursing professionals was evidenced, which supports the lack of training reported in the interviews, contrasting with the increased encouragement to apply the bundle during the pandemic. In practice, this may represent inconsistent care and reinforces the need for training teams, since feeling encouraged to apply it may result in greater interest in learning. However, this was a period marked, at times, by greater adherence to protective measures, resulting in a reduction in healthcare-associated infections, and, at times, by relaxation and an increase in HAI rates.[19,20]

The practices selected for knowledge assessment correspond to six care procedures that make up the bundle: 1 - positioning of the headboard between 30º and 45º; 2 - checking the cuff pressure between 20-30 cmH2O; 3 - oral hygiene with chlorhexidine 0.12%; 4 - respiratory and motor physical therapy; 5 - care with the aspiration of secretions; 6 - interruption of sedative infusion.[11,21]

The study showed that nursing professionals at the institution have little knowledge about the elements that make up the VAP prevention bundle, which certainly limits their ability to implement prevention actions. Some of the components of the bundle are routine nursing care, such as oral hygiene and positioning. However, it is necessary to understand these actions as part of the bundle of VAP preventive measures. A study conducted in Australia,[16] which assessed the knowledge of specialist nurses in ICUs, identified that the most mentioned element of the bundle for VAP prevention was positioning (90.9), unlike our study, in which this element was mentioned by only 28% of professionals, referred to here as elevated headboard, a highly effective nursing intervention for VAP prevention.[22]

Elevated headboard position, oral hygiene and adequate maintenance of cuff pressure represent the main preventive measures for subglottic aspiration, one of the most common causes of VAP.[4,11] They also represent routine nursing interventions and, even so, were rarely mentioned as measures to prevent VAP. Furthermore, the assessment of patients, which involves the level of consciousness and oxygenation, is also part of nursing routine, which, together, covers the other items in the bundle, such as the possibility of extubation, awakening/reduction of sedation and adequate ventilation system maintenance. However, despite being nursing interventions, they were not mentioned as components of the VAP prevention bundle.

Considering all the elements of the bundle, in general, studies have shown a low level of knowledge among professionals, which certainly impacts adherence to the VAP bundle and incidence.[15,16] A study conducted in Brazil found that the frequency of adherence to the bundle by nursing professionals was significant only for three proposed items, namely the position of the headboard between 30º and 45º, care with suction of secretions and respiratory and motor physical therapy, with the overall adherence rate being 77.4%; therefore, no events of complete bundle implementation were observed.[23] Such data support the results of this study, and alert ICU managers to team continued education.

A study conducted in Porto Alegre (RS) assessed nursing adherence to the VAP prevention bundle and the incidence rate before and after implementing a continuing education program. The data revealed an increase in adherence to all components of the interventions proposed in the bundle and, consequently, a reduction in VAP incidence rates, which demonstrates that continuing education is an important tool for maintaining adherence to the VAP prevention bundle in favor of the safety of critically ill patients in the ICU.[8] It is worth noting that, in the present study, physical therapists were more prepared, when compared to the nursing team, in relation to all elements of the VAP prevention bundle. It is also worth noting that care should be provided in a multidisciplinary manner, resulting in substantial improvements in healthcare.[17]

Logistic regression showed that, in the present study, age was inversely related to knowledge of bundle elements, suggesting that younger professionals tend to have more knowledge; this may be due to the recent inclusion of topics related to patient safety, especially in HAI prevention, in healthcare professional training.[24-25] Therefore, it is essential to recognize the importance of HAI prevention and control actions in professional training, ensuring this content in the training curriculum for healthcare professionals, as well as prioritizing professional training, providing instruments for monitoring adherence to the bundle, in order to reduce the incidence of VAP which, especially for patients with COVID-19, culminates in unfavorable outcomes.

This study has limitations, such as the distribution of participants from the physical therapy team being smaller than that of the nursing team, but it represents the proportion between the professional categories. Self-reported knowledge may also contribute to limitations of this study, as it may not reflect real knowledge on the subject, indicating the need for further research with more objective assessments of knowledge.

Although this study was conducted in the context of the COVID-19 pandemic, the results have the potential to qualify ICU care in different contexts, and are especially transferable to other infectious or non-infectious respiratory impairment syndromes that may increase the demand for ICUs, signaling the need for training in

the face of new hires, and the maintenance of a qualified team to apply VAP prevention measures.

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AUTHORS' CONTRIBUTIONS

Hélio Galdino-Júnior contributed to the conception, study design and project administration, bibliographic research, interpretation and description of results, manuscript writing and article critical review. **George Oliveira** contributed to the interpretation and description of results, statistical analysis, manuscript writing and final review. **Ana Clara Alves Campos** contributed to bibliographic research, field data collection, abstract writing, methodology, interpretation of results, conclusions. **Jéssica de Oliveira Montebelo** contributed to bibliographic research, field data collection, abstract writing, methodology, interpretation of results, conclusions.

All authors have approved the final version to be published and are responsible for all aspects of the work, including ensuring its accuracy and integrity.

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Revista de Epidemiologia e Controle de Infecção

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ORIGINAL ARTICLE

Healthcare-associated infections caused by *Candida* spp. in critical infants: a look at environmental surfaces

Infecções relacionadas à assistência à saúde causadas por Candida spp. em neonatos críticos: uma análise das superfícies ambientais

Infecciones asociadas a la atención sanitaria causadas por Candida spp. en neonatos críticos: un análisis de las superficies ambientales

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Corresponding Author:
Ralciane de Paula Menezes
ralciane@ufu.br

Address: Curso Técnico em Análises Clínicas, Escola Técnica de Saúde, Universidade Federal de Uberlândia, Rua Piauí, 776, Bairro Umuarama, Uberlândia, Minas Gerais, Brasil.

Priscila Guerino Vilela Alves[1];
Isadora Caixeta da Silveira Ferreira[1];
Ralciane de Paula Menezes[1];
Mário Paulo Amante Penatti[1];
Reginaldo dos Santos Pedroso[1];
Denise Von Dolinger de Brito Röder[1];

[1] *Universidade Federal de Uberlândia, Uberlândia, MG, Brasil.*

ABSTRACT

Background and Objectives: invasive fungal infections entail high morbidity and mortality rates in Neonatal Intensive Care Units (NICUs) and are accompanied by an increasing prevalence of resistant isolates, highlighting hospital environments as the primary sources of contamination. This study identified *Candida* species in infants in a Brazilian NICU, assessed their clinical and laboratory conditions and characterized the isolates. **Methods:** *Candida* isolates from newborns (NBs) and environments were identified and analyzed for antifungal resistance, virulence factors, and molecular relationships. **Results:** four NBs presented invasive candidiasis, such as *C. albicans* (2 NBs), *C. glabrata* (1 NB), and *C. parapsilosis sensu stricto* (1 NB). All NBs were extremely premature (<29 weeks) and had used at least one invasive device. Two clinical isolates demonstrated resistance, one to fluconazole (*C. parapsilosis* sensu stricto) and the other to micafungin (*C. glabrata*). Five environmental isolates were identified as *C. parapsilosis sensu stricto*, and one of them showed to be fluconazole susceptible-dose dependent. Biofilm was the only virulence factor produced by all nine isolates. Molecular analysis revealed high similarity between one environmental isolate and one clinical isolate of *C. parapsilosis sensu stricto*. **Conclusions:** the results indicated the presence of *Candida* species in infants and NICU environments, with some demonstrating *in vitro* resistance to fluconazole and micafungin. All isolates produced biofilm. A notable genetic similarity was observed between some environmental and clinical isolates, suggesting the environment as a possible source of infection.

Keywords: *Invasive Fungal Infections. Cross Infection. Infection Control. Infant Health.*

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RESUMO

Justificativa e Objetivos: infecções fúngicas invasivas acarretam elevada morbimortalidade em Unidades de Terapia Intensiva Neonatal (UTINs) e estão acompanhadas de um aumento de isolados resistentes, evidenciando o ambiente hospitalar como fonte primordial de contaminação. Este estudo identificou espécies de *Candida* em neonatos em uma UTIN brasileira, avaliou suas condições clínicas e laboratoriais e caracterizou os isolados. **Métodos:** isolados de *Candida* de recém-nascidos (RNs) e do ambiente foram identificados e analisados quanto à resistência antifúngica, fatores de virulência e relação molecular. **Resultados:** quatro RNs apresentaram candidíase invasiva, como *C. albicans* (2 RNs), *C. glabrata* (1 RN) e *C. parapsilosis sensu stricto* (1 RN). Todos RNs eram extremamente prematuros (<29 semanas) e utilizaram algum dispositivo invasivo. Dois isolados clínicos demonstraram resistência, um ao fluconazol (*C. parapsilosis sensu stricto*) e o outro à micafungina (*C. glabrata*). Cinco isolados ambientais foram identificados como *C. parapsilosis sensu stricto*, e um deles mostrou susceptibilidade dependente da dose ao fluconazol. O biofilme foi o único fator de virulência produzido pelos nove isolados. A análise molecular revelou alta similaridade entre um isolado ambiental e um clínico de *C. parapsilosis sensu stricto*. **Conclusões:** os resultados indicaram a presença de espécies de *Candida* em neonatos e no ambiente da UTIN, com algumas demonstrando resistência *in vitro* ao fluconazol e à micafungina. Todos isolados produziram biofilme. Foi observada uma notável similaridade genética entre alguns dos isolados ambientais e clínicos, sugerindo o ambiente como uma possível fonte de infecção.

***Descritores**: Controle de Infecções. Infecções Fúngicas Invasivas. Infecção Hospitalar. Saúde do Lactente.*

RESUMEN

Justificación y Objetivos: las infecciones fúngicas invasivas conllevan altas tasas de morbilidad y mortalidad en las Unidades de Cuidados Intensivos Neonatales (UCINs) y están acompañadas por un aumento en la prevalencia de aislamientos resistentes, destacando el ambiente hospitalario como la principal fuente de contaminación. Este estudio identificado las especies de *Candida* en neonatos en una UCIN brasileña, evaluó sus condiciones clínicas y de laboratorio y caracterizó los aislamientos. **Métodos:** se identificaron y analizaron los aislamientos de *Candida* de recién nacidos (RNs) y del ambiente en relación con la resistencia antifúngica, los factores de virulencia y las relaciones moleculares. **Resultados:** cuatro RNs presentaron candidiasis invasiva, como *C. albicans* (2 RNs), *C. glabrata* (1 RN) y *C. parapsilosis sensu stricto* (1 RN). Todos los RNs eran extremadamente prematuros (<29 semanas) y habían utilizado al menos un dispositivo invasivo. Dos aislamientos clínicos demostraron resistencia, uno al fluconazol (*C. parapsilosis sensu stricto*) y el otro a la micafungina (*C. glabrata*). Cinco aislamientos ambientales se identificaron como *C. parapsilosis sensu stricto*, y uno de ellos mostró susceptibilidad dependiente de la dosis al fluconazol. El biofilm fue el único factor de virulencia producido por los nueve aislamientos. El análisis molecular reveló una alta similitud entre un aislamiento ambiental y uno clínico de *C. parapsilosis sensu stricto*. **Conclusión:** los resultados indicaron la presencia de especies de *Candida* en neonatos y en el ambiente de la UCIN, con algunas mostrando resistencia *in vitro* al fluconazol y a la micafungina. Todos los aislamientos produjeron biofilm. Se observó una notable similitud genética entre algunos aislamientos ambientales y clínicos, lo que sugiere que el ambiente podría ser una posible fuente de infección.

***Palabras Clave:** Infecciones Fúngicas Invasoras. Infección Hospitalaria. Control de Infecciones. Salud del Lactante.*

INTRODUCTION

Neonatal Intensive Care Units (NICUs) are environments where patients are vulnerable to various types of infections. Invasive fungal infections (IFIs) stand out because they contribute to morbidity and mortality, especially in cases of prematurity, low birth weight (LBW) and immaturity of the immune system.[1-4] In this context, the *Candida* genus emerges as the predominant fungal agent with a high lethality rate ranging from 30-78%.[5-7]

The incidence of invasive candidiasis (IC) in NICUs ranges between 0.5% and 20%, with *Candida albicans* being the most common species (55-60%).[1,2,8] The increase in infections by non-*albicans Candida* (NAC) species has been described in the literature, and *C. parapsilosis* is among the most prevalent species that cause candidemia worldwide. In Brazil, *C. parapsilosis* accounts for more than 20% of *Candida* species isolated in blood cultures.[1] In recent years, the occurrence of fluconazole-resistant *C. parapsilosis* strains has expanded in the workplace around the world, persisting in several hospital niches, resulting in higher mortality rates (50-63.8%).[1]

C. parapsilosis causes outbreaks in NICUs, linked to increased morbidity and mortality.[1,7] The high incidence of these infections suggests failures in hand hygiene among healthcare professionals and in hospital environments.[3,9] Studies have shown genetic similarity between *C. parapsilosis* isolates from patients and NICU environments,[2] indicating a common source of infection.[9]

The lack of adequate sanitation, the prolonged presence of fungal species in hospital environments and the ability to produce factors that facilitate infection, evasion of the immune system and adherence to the host surfaces have a major impact on morbidity and mortality

due to *Candida* spp. in NICUs.[1,5,8] Among the virulence factors, the production of hydrolytic enzymes, such as proteases, lipases, and phospholipases, as well as the formation of biofilms, stands out.[3,5,10,11]

The present study aims to identify *Candida* species isolated from newborns with bloodstream infections (BSIs) and those isolated in NICU environments. Additionally, we assessed the clinical and laboratory conditions of newborns (NBs) with BSI and characterized the isolates through phenotypic and genotypic tests.

METHODS

Patients and study location

The study was conducted in a NICU of a high-complexity public hospital in southeastern Brazil, which has 20 intensive and intermediate care beds. Infants with laboratory confirmation of IC were included, and demographic and epidemiological data were obtained from medical records. These NBs were monitored daily by the National Healthcare Safety Network (NHSN) epidemiological surveillance system[12] from admission to discharge or death within a period of one year.

Clinical and environmental sample collection and isolate identification

Blood samples were obtained and identified in the hospital's Clinical Analysis Laboratory by traditional methods using the BACT/Alert® system and confirmed by Vitek® systems (bioMérieux–Durham, USA) between March and December 2018.

Samples from NICU environments were collected three times a day, at the beginning of each of the three work shifts, between March and December 2018, according to the protocol described by Menezes *et al*.[13] The samples were obtained from high-touch surfaces (incubators, monitor tables, respirator monitors, infusion pumps, vital signs monitors, NICU access doors, soap dishes, paper towel holders, tap nozzles, cabinet drawers, light switches, medicine refrigerator doors, medicine preparation tables and bath sink drains).[14]

For this purpose, swabs (Plastlabor, Rio de Janeiro, Brazil) pre-moistened with 0.9% sodium chloride were used, which were rubbed vigorously in areas delimited by sterile molds. In the laboratory, the collection material was vortexed, and 0.2 mL of the solution was seeded on plates containing Sabouraud Dextrose Agar (SDA - Isofar, Duque de Caxias, RJ, Brazil) with the addition of chloraphenicol, and on plates with agar chromogenic for *Candida* (Himedia, Mumbai, India). These were incubated at 35°C for up to 72 hours. Fungal isolates were identified using the matrix-assisted laser desorption ionization (MALDI) technique, followed by detection on a time-of-flight (TOF) analyzer, MALDI TOF (Bruker MALDI Biotyper 4.0).

Antifungal resistance profile

The resistance profile of isolates was determined using the broth microdilution technique, as recommended by the Clinical and Laboratory Standards Institute (CLSI) in documents M27-A3-S3 and M27-S4.[15,16] The antifungals assessed were fluconazole (Fluoxol, La Paz, Bolivia), amphotericin B (Cristalia, São Paulo, Brazil) and micafungin (Raffo, Buenos Aires, Argentina). The test plates were incubated at 35ºC for 24 hours, and the reading was taken using a spectrophotometer with a wavelength of 490 nm. The tests were carried out in duplicate, in independent experiments, and the *C. parapsilosis* ATCC 22019 strain was used as a technique control.

The Minimum Inhibitory Concentration (MIC) was defined as the lowest concentration of the antifungal that resulted in a 50% reduction in yeast cell growth compared to fluconazole and micafungin, with 90% for amphotericin B.[17,18] The interpretation of the MIC and the cut-off points for each antifungal followed CLSI documents M59, M60 and M27-S4[19,20] guidelines as well as the criteria established by Pfaller and Diekema (2012).[21]

Biofilm formation assessment

Biofilm biomass production (0.5% crystal violet) was assessed according to the protocol by Costa-Orlandi *et al*. (2014),[22] with modifications. Biofilm metabolic activity (reduction of Aldrich, St. Louis, MO, USA) was carried out using the methodology of Pierce *et al*. (2008).[23] Spectrophotometer readings were at 570 nm for biomass and 490 nm for biofilm metabolic activity.

The results were classified based on the cut-off point of each strain into low, moderate, and high biofilm production for biomass and metabolic activity, following criteria from Marcos-Zambrano *et al*. (2014).[24] For biomass, the following optical deviation (OD) was considered: low<0.44; moderate=0.44-1.17; high>1.17. For metabolic activity, the OD considered were low<0.097, moderate=0.097–0.2, high>0.2. Negative controls were wells containing only Roswell Park Memorial Institute (RPMI) broth. The tests were performed in quadruplicate and repeated three times independently.

Extracellular hydrolytic enzyme and hemolytic activity assessment

Assessment of *Candida* spp.'s ability to produce the extracellular hydrolytic enzymes DNAse, phospholipase and proteinase, and hemolytic activity followed the protocol by Riceto *et al*. (2015).[10] The tests were performed in duplicate in independent experiments, and the analysis and interpretation of results were carried out as proposed by Menezes *et al*. (2019).[25]

Molecular analysis

Genetic similarity analysis was performed by random amplified polymorphic DNA (RAPD-PCR), and the extraction of the genomic DNA of isolates was carried out from cultures in SDA medium (24 hours) at 35ºC. The primer oligonucleotides used were OPA9 (5'-GGGTAACGCC-3'), OPA18 (5'-AGCTGACCGT-3'), OPB11 (5'-GTAGACCCGT-3') and OPG17 (5'-ACGACCGACA-3') (Operon Technologies Inc.). Reactions and amplification products were conducted according to the protocol established by Riceto *et al*. [2017].[26]

RESULTS

Sample characterization

During the study period, seven NBs presented BSI, and of these, four were due to *Candida* species, such as *Candida glabrata* (NB 1), *C. albicans* (NB 2 and NB 3) and *C. parapsilosis sensu stricto* (NB 4). All NBs with *Candida* BSI were biological male, extremely premature (<29 weeks) and used at least one invasive device. The average length of hospital stay was 70 days, and the NB with *C. parapsilosis sensu stricto* infection died (Table 1).

Five isolates were recovered from environmental samples, all identified as *C. parapsilosis sensu stricto*. They were obtained from the surface of an incubator table (sample 2A), from the inside of two incubators (samples 3A and 4A), from a drawer (sample 7A) and from a bench used for preparing medications (sample 8A) (Table 2; Figure 1).

Table 1. Clinical characteristics of newborns with *Candida* spp. bloodstream infection in a Neonatal Intensive Care Unit. Uberlândia, Minas Gerais, Brazil, 2024.

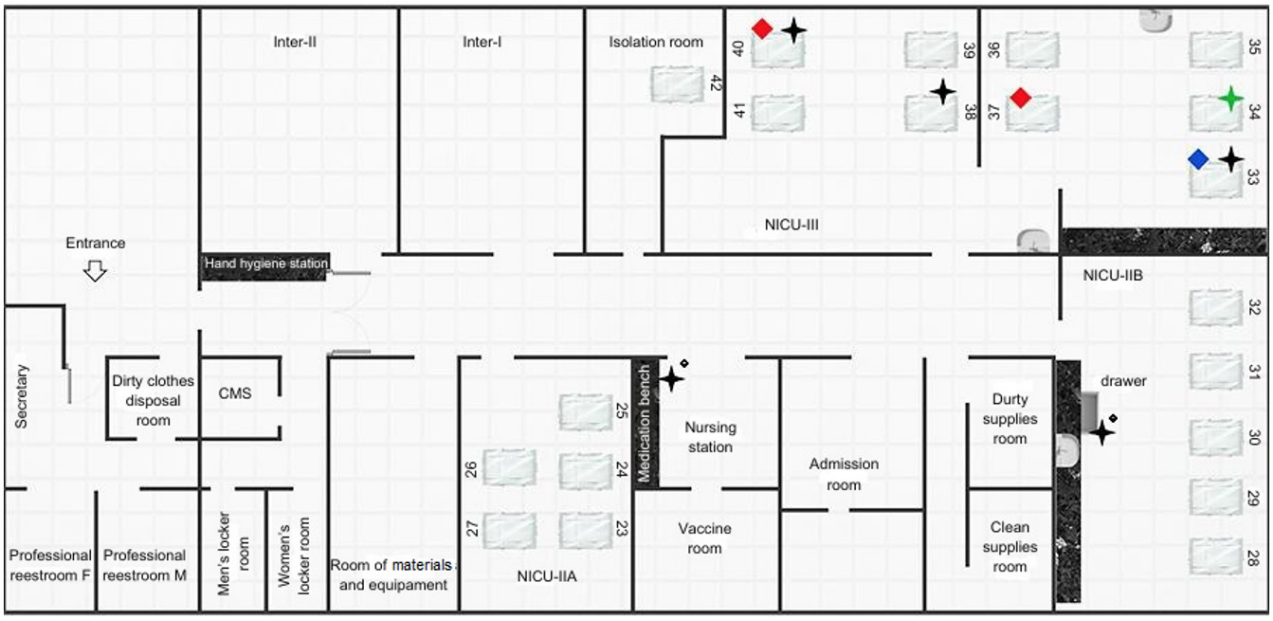
Characteristics	NB 1	NB 2	NB 3	NB 4
Gestational age (weeks)	24.6	24.3	29	25.3
Birth weight (grams)	610	696	1,485	645
Reason for hospitalization	Respiratory distress syndrome; extreme low weight	Respiratory distress syndrome; extreme low weight	Respiratory distress syndrome; extreme low weight	Congenital malformation; extreme low weight
Gastrointestinal tract surgery	NI	NI	NI	EAC
Invasive devices (days of use)				
PICC	35	47	18	15
UVC	3	8	NI	NI
MV	55	77	10	8
PN	23	20	14	12
PVC	14	23	NI	NI
Antifungals (days of use)				
Fluconazole				
Use prior to infection	16	NI	NI	NI
Use after infection	NI	10	22	6
Micafungin				
Use prior to infection	NI	NI	NI	NI
Use after infection	18	NI	NI	6
Length of hospitalization in the NICU (days)	87	126	50	15
Length of hospitalization before BSI (days)	21	5	10	1
BSI date	9/3/18	3/11/18	7/14/18	9/24/18
Outcome	Discharge	Discharge	Discharge	Death

Note: BSI - bloodstream infection; EAC - esophageal atresia correction; NI - no information; NB - newborn; NICU - neonatal intensive care unit; MV - mechanical ventilation; PN - parenteral nutrition; PICC - peripherally inserted central catheter; PVC - peripheral venous catheter; UVC - umbilical venous catheter.

Table 2. Phenotypic characteristics (biofilm production and susceptibility to antifungals) of *Candida* species isolated from environments and bloodstream of infants in the Neonatal Intensive Care Unit. Uberlândia, Minas Gerais, Brazil, 2024.

Species	Local	Collection date	VC	VTT	Amphotericin B MIC (µg/ mL)	Fluconazole MIC (µg/ mL)	Micafungin MIC (µg/ mL)
C. parapsilosis sensu stricto 2A	Surface in incubator table	3/19/18	HBP	HAM	0.50	2.00	1.00
C. parapsilosis sensu stricto 3A	Part internal incubator	3/19/18	MBP	HAM	0.50	1.00	2.00
C. parapsilosis sensu stricto 4A	Part internal incubator	3/19/18	MBP	HAM	0.50	4.00	1.00
C. parapsilosis sensu stricto 7A	Drawer cabinet NICU IIB•	6/26/18	MBP	HAM	0.50	0.50	2.00
C. parapsilosis sensu stricto 8A	Medication bench•	6/26/18	HBP	HAM	0.25	1.00	2.00
C. glabrata (NB 1)	Blood	9/3/18	HBP	HAM	1.00	2.00	2.00
C. albicans (NB 2)	Blood	3/11/18	HBP	HAM	0.50	0.50	0.03
C. albicans (NB 3)	Blood	7/14/18	MBP	HAM	0.50	1.00	0.03
C. parapsilosis sensu stricto (NB 4)	Blood	9/24/18	MBP	HAM	1.00	8.00	2.00

Note: HAM - high activity metabolic; HBP - high biomass production; MBP - moderate biomass production; MIC - Minimum Inhibitory Concentration; NICU - Neonatal Intensive Care Unit; VC - violet crystal; XTT - tetrazole salt; •isolates considered identical by the combined analysis of primers OPA09, OPA18, OPB11 and OPG17.



Note: C. albicans 1 and 2 (red diamonds), C. glabrata (blue diamond), and C. parapsilosis sensu stricto (green star), all of them u from the blood culture, and C. parapsilosis sensu stricto from the environment culture (black stars); • identical isolates.

Figure 1. Schematic representation of the Neonatal Intensive Care Unit and location of isolation of environmental and clinical samples included in the study. Uberlândia, Minas Gerais, Brazil, 2024.

Antifungal susceptibility test

Two clinical isolates demonstrated resistance to at least one of the antifungals tested: *C. parapsilosis sensu stricto* to fluconazole and *C. glabrata* to micafungin. Furthermore, one environmental isolate (4A) showed to be fluconazole susceptible-dose dependent (SDD) (4µg/mL). Table 2 describes MIC values.

Virulence factor production assessment

All isolates demonstrated the ability to form biofilm *in vitro*, exhibiting high metabolic activity. Furthermore, 44.4% (4/9) were classified as producing biomass at high levels, including two (22.2%) isolates from environments (2A and 8A). The production of extracellular hydrolytic enzymes (DNAse, phospholipase and proteinase) or hemolytic activity was not observed in any of the isolates (Table 2).

Isolate genetic similarity determination

Molecular analysis revealed a cluster (A) with five highly similar *C. parapsilosis sensu stricto* isolates (Sj>80%). This group included four environmental samples (2A, 3A, 7A, 8A) and one clinical sample (NB 4) (Figure 2). Two environmental samples (7A and 8A) were considered identical. All highly similar samples from environments were collected in the first two moments, with an interval of 99 days between the first and second collection. Clinical sample was collected 90 days after the last environmental isolates (7A and 8A) (Table 2).

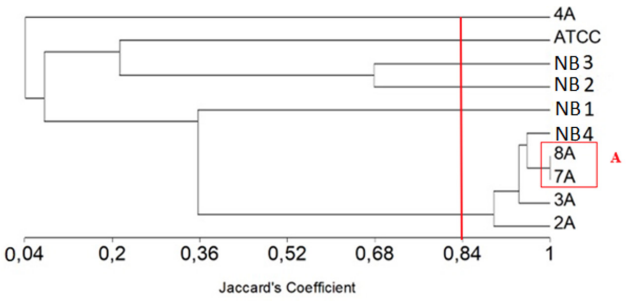


Figure 2. Dendrogram of *Candida* spp. isolates originating from Neonatal Intensive Care Unit environments and the bloodstream of infants with combined analysis of primers OPA09, OPA18, OPB11 and OPG17. Uberlândia, Minas Gerais, Brazil, 2024.

DISCUSSION

IC is often underdiagnosed, with an estimated non-detection rate of between 30% and 70%.[27] The lack of epidemiological data in NICU, especially in developing countries, is evident. Although the importance of hospital environments in the spread of microorganisms, including resistant ones, is recognized,[27] there are few studies on the presence of pathogenic fungi in this context, espe-

cially in NICUs. However, studies carried out in countries in Latin America, Africa and Asia have demonstrated the presence of *Candida* spp. in NICUs, highlighting it as a potential source of healthcare-associated infections (HAIs).

In this study we identified three *Candida* species causing IC in the four NBs (*C. albicans*, *C. parapsilosis sensu stricto* and *C. glabrata*) and one in NICU environments (*C. parapsilosis sensu stricto*). The relationship between *C. parapsilosis* infections and NICU environments indicates the negative impact on NB survival, especially when inadequate hygiene measures contribute to the transmission of the pathogen microorganisms.[2,3,9]

Maintaining a clean environment and applying rigorous hand hygiene measures, as well as reinforcing cleaning, disinfection protocols and monitoring the effectiveness of these practices, is crucial to ensuring patient safety, mainly when there are risks of outbreaks caused by resistant pathogens.[7]

In Brazil, some studies have shown a varied distribution of *Candida* species causing IC encompassing BSIs and deep-seated candidiasis, according to different regions of the country.[5] In the northeast, *C. albicans* (35.3%), *C. tropicalis* (27.4%), *C. parapsilosis* (21.6%) and *C. glabrata* (11.8%) were the most frequent. In the north, *C. albicans* predominated (44%), followed by *C. glabrata* (19%), *C. tropicalis* (19%) and *C. parapsilosis* (14%). In southeastern Brazil, a frequency of 81.1% was reported for *C. parapsilosis sensu stricto*.[5] This highlights the predominance of NAC species in the country. *Candida* spp. has already been reported in several hospital areas, including the hands of healthcare professionals. Although most *Candida* species infections are endogenous, hospital environments can also be a source, especially in cases of critically ill patients.[14] In our study, *C. parapsilosis sensu stricto* was isolated in NICUs from high-touch surfaces, what is of concern due to the potential increased risk of cross-contamination or nosocomial transmission. The inherent vulnerability of premature NBs due to the immaturity of the immune system and the fragility of epithelial barriers makes them more prone to IC.[6] All NBs in the study were born at less than 30 weeks of gestation and weighing less than 1,500 grams. Generally, IC manifests itself around the fourth week of life;[3] however, in this study, the average time for IC development ranged from 1 to 21 days, with *C. parapsilosis* manifesting more quickly than *C. glabrata*.

The predominance of *C. parapsilosis* can be explained by its colonization in the skin microbiota of healthy individuals and its ability to adhere to surfaces, by the ability to form biofilm (all isolates of this study formed biofilm). A previous study showed *C. parapsilosis* on inanimate surfaces, hands, and infection in the same NICU, and the isolates demonstrated phenotypic and genetic similarities, revealing this microorganism's ability to remain in the unit for months, suggesting infections through cross-transmission or even intestinal translocation, supporting our results.[3]

C. parapsilosis is prone to colonizing intravascular catheters and proliferating in individuals using parenteral nutrition.[2,9] The four infants analyzed in this study used peripherally inserted central catheter and received parenteral nutrition therapy. One NB had a congenital malformation in the esophagus and was extremely LBW (645 grams), affected by *C. parapsilosis sensu stricto* infection died six days after diagnosis of candidemia. That strain showed resistance to fluconazole, high metabolism in the biofilm, and demonstrated genetic similarity with environmental samples from NICUs (isolated from the drawer, and from the medication handling bench), despite having differences in resistance to antifungals. This result highlights the complexity of interactions between environmental and clinical strains, and the importance of surveillance and understanding resistance factors.

The *in vitro* resistance in *C. parapsilosis* from IC has been reported in several countries, including Brazil,[3,7] being associated with the occurrence of outbreaks.[7] The occurrence of invasive infections by fluconazole-resistant *C. parapsilosis* in NICUs is a significant concern due to the negative impact on patient prognosis and neonatal mortality rates,[7] considering that fluconazole is the first-choice antifungal for IC treatment in NICUs in different countries. The reduced susceptibility to fluconazole of *C. parapsilosis* isolated from the NICU environment study has been previously reported,[4,7] and draws attention because it is a unit that cares for critically ill patients and the occurrence of infections due to environmental isolates be something possible. In our study, the isolate, besides showing dose-dependent susceptibility to fluconazole, had a moderate to high capacity for biofilm formation, what is related to protection against antifungal drugs and the immune response, in addition to enabling survival in environments hospital conditions, also resisting the action of disinfectants and desiccation.[7] Biofilm forming by environmental isolates has been previously related.[2]

Strategies such as care protocols, efficient management of antimicrobials and hygiene practices are crucial to prevent infections in NICUs.[7] Given the vulnerability of infants to infections due to the immaturity of the immune system and the frequent use of invasive devices,[6] this study provides clinical and environmental data on infections by *Candida* in NICUs. Furthermore, the research highlights the scarcity of information on this topic, highlighting the relevance of this study in the epidemiology of HAIs caused by *Candida* spp. and the need for more research in this area.

In conclusion, this study identified *Candida* species in infants and in NICU environments, demonstrating resistance to fluconazole and micafungin, in addition to all isolates forming biofilm. A high genetic similarity was observed between some environmental and clinical isolates, suggesting environments as possible sources of infection. These results are in line with findings in literature, reinforcing the importance of environmental surveillance, rigorous hand hygiene practices and frequent disinfection of hospital environments, especially in high-touch areas, such as surfaces of incubators.

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AUTHORS' CONTRIBUTIONS

Priscila Guerino Vilela Alves contributed to the literature search, writing of the abstract, introduction, methodology, discussion, interpretation and description of results, preparation of tables, conclusions, review and statistics. **Isadora Caixeta da Silveira Ferreira** contributed to the project administration, literature search, writing of the abstract, introduction, methodology, discussion, interpretation and description of results, conclusions, review and statistics. **Ralciane de Paula Menezes** contributed to the writing of the abstract, methodology, interpretation of results, conclusions, review and statistics. **Mário Paulo Amante Penatti** contributed to the writing of the abstract, review and statistics. **Reginaldo dos Santos Pedroso** contributed to the writing of the abstract, review and statistics. **Denise Von Dolinger de Brito Röder** contributed to the project administration, literature search, writing of the abstract, introduction, methodology, discussion, interpretation and description of results, conclusions, review and statistics.

All authors approved the final version to be published and are responsible for all aspects of the work, including ensuring its accuracy and integrity.

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Hospital Santa Cruz

ORIGINAL ARTICLE

Prevalence of COVID-19 among healthcare workers before and after vaccination

Prevalência de COVID-19 entre trabalhadores da saúde antes e depois de vacinação

Prevalencia de COVID-19 entre trabajadores de salud antes y después de la vacunación

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Corresponding Author:
Karina Pinheiro Teixeira dos Reis
karinapinheirot@gmail.com

Address: Curitiba, Paraná, Brasil.

Karina Pinheiro Teixeira dos Reis[1,2];
Mirelle de Oliveira Saes[1];
Ivy Bastos Ramis[1];

[1] *Universidade Federal do Rio Grande, Programa de Pós-graduação em Ciências da Saúde, Rio Grande, RS, Brasil.*
[2] *Hospital Universitário Dr. Miguel Riet Corrêa Jr. – HU - Furg/ EBSERH, RS, Brasil.*

ABSTRACT

Background and Objectives: healthcare workers are at high risk of acquiring infections during disease outbreaks. Therefore, this study aimed to determine the prevalence of COVID-19 among vaccinated and unvaccinated healthcare workers. **Methods:** a cross-sectional and observational study that assessed cases of flu syndrome that occurred between March 2020 and December 2021 in healthcare workers vaccinated and unvaccinated with CoronaVac or Astrazeneca in a hospital in the extreme south of Brazil. The study included cases of flu syndrome characterized and monitored by the institution's occupational health sector and who underwent diagnostic tests by RT-PCR for SARS-CoV-2. The Prevalence Ratio estimated by Poisson regression analysis with variance adjustment was used to verify the factors and strengths of the associations. **Results:** a total of 1,088 cases of flu syndrome that occurred in healthcare workers between 2020 and 2021 were assessed. When adjusted for sex, age, role, sector, type of vaccine or previous diagnosis of COVID-19, the prevalence of COVID-19 among cases of unvaccinated workers was 51.5% (95% CI: 46.5- 56.5) and 32.1% (95% CI: 25.3-38.8) among unvaccinated workers. Moreover, COVID-19 vaccination reduced the prevalence of new infections by 33% (PR: 0.67; 95% CI: 0.56-0.81). **Conclusion:** COVID-19 vaccination significantly reduced the prevalence of COVID-19 among healthcare workers, regardless of sex, age, sector, role, type of vaccine or previous diagnosis of COVID-19.

Keywords: *COVID-19. SARS-CoV-2. Health Personnel. Vaccines.*

RESUMO

Justificativa e Objetivos: os profissionais de saúde correm alto risco de adquirir infecções durante surtos de doenças. Assim, o objetivo deste estudo foi determinar a prevalência de COVID-19 entre profissionais de saúde vacinados e não vacinados. **Métodos:** estudo observacional e transversal, que avaliou casos de síndrome gripal ocorridos

entre março de 2020 e dezembro de 2021 em trabalhadores da saúde vacinados e não vacinados com CoronaVac ou Astrazeneca em um hospital do extremo sul do Brasil. O estudo incluiu casos de síndrome gripal caracterizados e acompanhados pelo setor de saúde ocupacional da intuição e que realizaram testes diagnósticos por RT-PCR para SARS-CoV-2. A medida da Razão de Prevalência estimada pela análise de regressão de Poisson com ajuste de variância foi utilizada para verificar os fatores e as forças das associações. **Resultados:** foram avaliados 1.088 casos de síndrome gripal ocorridos em profissionais de saúde entre 2020 e 2021. Quando ajustada por sexo, idade, função, setor, tipo de vacina ou diagnóstico prévio de COVID-19, a prevalência de COVID-19 entre os casos de profissionais não vacinados foi de 51,5% (IC 95%: 46,5-56,5) e de 32,1% (IC 95%: 25,3-38,8) entre profissionais não vacinados. Além disso, a vacinação para a COVID-19 reduziu a prevalência de novas infecções em 33% (RP: 0,67; IC 95%: 0,56-0,81). **Conclusão:** a vacinação para a COVID-19 reduziu significativamente a prevalência da COVID-19 entre os profissionais de saúde, independentemente do sexo, idade, setor, função, tipo de vacina ou diagnóstico prévio de COVID-19.

Descritores: *COVID-19. SARS-CoV-2. Profissionais da Saúde. Vacinas.*

RESUMEN

Justificación y Objetivos: los trabajadores de la salud tienen un alto riesgo de contraer infecciones durante los brotes de enfermedades. Por tanto, el objetivo de este estudio fue determinar la prevalencia de COVID-19 entre profesionales sanitarios vacunados y no vacunados. **Métodos:** estudio observacional y transversal, que evaluó casos de síndrome gripal ocurridos entre marzo de 2020 y diciembre de 2021 en trabajadores de la salud vacunados y no vacunados con CoronaVac o Astrazeneca en un hospital del extremo sur de Brasil. El estudio incluyó casos de síndrome gripal caracterizados y monitoreados por intuición del sector de salud ocupacional y a los que se les realizaron pruebas diagnósticas por RT-PCR para SARS-CoV-2. Para verificar los factores y las fortalezas de las asociaciones, se utilizó la medida de la Razón de Prevalencia estimada mediante análisis de regresión de Poisson con ajuste de varianza. **Resultados:** se evaluaron 1.088 casos de síndrome gripal ocurridos en profesionales de la salud entre 2020 y 2021. Al ajustar por sexo, edad, función, sector, tipo de vacuna o diagnóstico previo de COVID-19, la prevalencia de COVID-19 entre los casos profesionales no vacunados fue de 51,5. % (IC 95%: 46,5-56,5) y 32,1% (IC 95%: 25,3-38,8) entre profesionales no vacunados. Además, la vacunación contra COVID-19 redujo la prevalencia de nuevas infecciones en un 33% (RP: 0,67; IC 95%: 0,56-0,81). **Conclusión:** la vacunación contra COVID-19 redujo significativamente la prevalencia de COVID-19 entre los trabajadores de la salud, independientemente de sexo, edad, sector, función, tipo de vacuna o diagnóstico previo de COVID-19.

Palabras Clave: *COVID-19. SARS-CoV-2. Personal de Salud. Vacunas.*

INTRODUCTION

Healthcare workers are at high risk of acquiring infections during outbreaks of contagious diseases, especially when there is little knowledge about the dynamics of infection.[1] In the period prior to COVID-19 vaccination, healthcare workers showed high rates of positivity for SARS-CoV-2, reaching a frightening 55.9% of symptomatic flu cases assessed.[2] Between March and April 2020, it was shown that healthcare workers were three times more likely to acquire SARS-CoV-2 when compared to the general population, even when these workers used adequate personal protective equipment, suggesting the urgent need for other infection control measures.[3]

Fortunately, throughout history, vaccines have been successfully developed for a number of potentially fatal diseases. Vaccines save lives by being able to stimulate the immune system, generating partial or total resistance against a particular pathogen. [4] In the COVID-19 scenario, vaccine development was carried out extremely quickly. The COVID-19 pandemic showed that, with the appropriate investments for input development, it is feasible to speed up many stages of vaccine development with a view to controlling diseases, preventing diseases and promoting health.[5]

However, although vaccines present a known strategy for disease control, population hesitancy to the COVID-19 vaccine is worrying reality. A global sample involving 23 countries including Brazil showed increasing hesitancy towards COVID-19 vaccination in at least eight countries. Belief in the vaccine's ability to prevent COVID-19, the vaccine's safety, and confidence in the vaccine development process remained strongly correlated with whether or not to accept the vaccine.[6]

Therefore, considering the high risk of SARS-CoV-2 transmission among healthcare workers, the development and initially emergency approval of vaccines to control COVID-19, and the constant population hesitancy regarding COVID-19 vaccination, it is of great importance to assess the impact of this vaccination on Brazilian healthcare workers. In this regard, this study aimed to determine the prevalence of COVID-19 among healthcare workers vaccinated and unvaccinated for COVID-19 and associated variables.

METHODS

This is a cross-sectional and observational study

that assessed cases of flu syndrome that occurred between March 2020 and December 2021 in healthcare workers from a highly complex hospital that has approximately 1,000 healthcare workers, with 231 beds exclusively for users of the public health system, in the municipality of Rio Grande, southern Brazil.

The institution initially offered the CoronaVac vaccine and later the Astrazeneca vaccine, and it was recommended that a second dose be of the same type as the first dose received. At the study site, the vaccines were administered from January 2021 according to the manufacturer's recommendations, with CoronaVac having an interval of 28 days between the first and second doses and Astrazeneca having an interval of 12 weeks (approximately three months). The hospital's occupational health sector (OHS) was responsible was responsible for administering the vaccines to professionals, monitoring the cases of flu syndrome developed by the institution's healthcare workers as well as scheduling and monitoring the results of tests for diagnosis of COVID-19 in these cases. Cases of flu syndrome were characterized by the OHS physician, considering the symptoms of fever, chills, sore throat, headache, cough, runny nose, smell or taste disturbances and gastrointestinal symptoms, following current recommendations of national health entities.

The study included cases of flu syndrome in professionals characterized by the OHS and who underwent diagnostic testing by RT-PCR for SARS-CoV-2 during the study period. The "vaccinated" group included cases of flu related to professionals who received at least one dose of the COVID-19 vaccine before the onset of symptoms of the reported flu episode. Cases with incomplete data were excluded from the analyses.

The variables assessed were sex, age, sector, role, previous diagnosis of COVID-19, vaccination (vaccinated or unvaccinated), type of vaccine (Astrazeneca or CoronaVac) as main exposure and result of the RT-PCR test for SARS-CoV-2 as an outcome.

Prevalence Ratio (PR) measure with 95% Confidence Interval, estimated by Poisson regression analysis with robust variance adjustment, was used to verify the factors and the strengths of the associations with the RT-PCR test result in the general sample. Analyses were performed using the Stata software 15, and a level of significance set at 5%.

This study was carried out in accordance with the required ethical standards (Resolutions 466/2012, 510/2016 and 580/2018 of the Ministry of Health), and approved by the *Universidade Federal do Rio Grande* Research Ethics Committee, under Opinion 4,980,106, on September 16, 2021, and Certificate of Presentation for Ethical Consideration 48156921.7.0000.5324.

RESULTS

A total 1,088 cases of flu syndrome were identified in healthcare workers, 581 flu cases in unvaccinated professionals and 507 in vaccinated professionals. Of the total sample, 83.2% were female, with a mean age of 41.3 years (standard deviation 9.0). More than half (70.6%) were from the nursing team, and most of them professionals in the Emergency/Inpatient/adult Intensive Care Unit (ICU) (38.7%) and surgical units (18.4%) (Table 1).

Table 1. Characteristics of healthcare workers with symptoms suggestive of COVID-19 (n:1,088).

Variables	%	95% CI*
Sex		
Male	16.8	14.7-19.2
Female	83.2	80.8-85.3
Age group		
1st tertile (21-36 years old)	35.7	32.9-38.6
2nd tertile (37-44 years old)	34.9	32.2-37.8
3rd tertile (45-66 years old)	29.4	26.8-32.2
Role		
Nurse/nursing technician and assistant	70.6	67.8-73.2
Physician	11.5	9.7-13.5
Physiotherapist	3.1	2.2-4.3
Others[a]	14.8	12.8-17.0
Sector		
Emergency/Inpatient/Adult ICU**	38.7	35.8-41.6
Surgical units	18.4	16.2-20.8
Pediatrics/neonatology	15.2	13.2-17.5
Others[b]	27.7	25.0-30.4
Vaccines		
CoronaVac	51.1	48.1-54.2
Astrazeneca	48.9	45.9-51.9
Previously confirmed COVID-19		
No	87.6	85.5-89.4
Yes	12.4	10.6-14.5

[a]Psychologist, pharmacist, pharmacy assistant or technician, radiology technician, laboratory/analysis technician, nutritionist and nutrition technician, speech therapist, optician, dentist, occupational therapist, physical educator, social worker, biologist, biomedical scientist, occupational safety technician.
[b]Outpatient clinics, rehabilitation service, nutrition, psychology, laboratories, pharmacy, imaging service, Central Sterile Supply Department, occupational health service, risk management, auditing, hotel management.
**Confidence Interval, **Intensive Care Unit.*

The prevalence of COVID-19 among the total cases monitored in the period was 25.3% (95% CI: 22.8-27.9), with a higher proportion among men (31.2%), older adults (26.6%) and medical workers (35.2%). We found a prevalence of 32.2% (95% CI: 28.5-36.1) of COVID-19 among flu cases of unvaccinated professionals and 17.4% (95% CI: 14.3-20.9) in cases of vaccinated professionals. Physician workers had a higher proportion of cases among vaccinated workers (29.6%) when compared to cases among unvaccinated physician workers or other vaccinated professional categories. Among unvaccinated flu cases, 38.4% of COVID-19 cases were identified among workers in surgical units, however in the vaccinated group only 15.9% of the cases were identified among workers in these units (Table 2).

When adjusted for sex, age, sector, role and previous diagnosis of COVID-19, the prevalence of COVID-19

Table 2. Prevalence of COVID-19 between the cases of flu syndrome in healthcare workers.

Variables	Overall (n: 1,088)		Unvaccinated (n: 581)		Vaccinated (n: 507)	
	%	95% CI*	%	95% CI*	%	95% CI*
Sex						
Male	31.2	24.8-38.3	40.6	31.1-50.9	20.7	13.3-30.7
Female	24.1	21.4-27.0	30.5	26.6-34.8	16.7	13.4-20.6
Age group						
1st tertile (21-36 years old)	25.3	21.2-29.8	32.4	26.4-39.1	16.9	12.0-23.2
2nd tertile (37-44 years old)	24.2	20.1-28.8	33.2	26.8-40.2	15.3	10.8-21.2
3rd tertile (45-66 years old)	26.6	22.0-31.7	30.9	24.6-38.1	20.9	14.8-28.5
Role						
Nurse/nursing technician and assistant	23.8	20.9-27.0	31.0	26.7-35.6	15.6	12.2-19.8
Physician	35.2	27.2-44.1	39.4	28.6-51.5	29.6	18.7-43.5
Physiotherapist	32.4	18.3-50.5	42.9	18.3-71.6	25.0	10.0-50.3
Others[a]	23.0	17.1-30.2	30.2	21.3-40.9	14.7	8.2-24.9
Sector						
Emergency/Inpatient/Adult ICU**	25.9	21.9-30.3	31.4	25.3-38.1	20.7	15.8-26.7
Pediatrics/neonatology	22.9	17.1-30.0	28.2	20.2-37.8	14.3	7.4-25.6
Surgical units	28.5	22.6-35.2	38.4	29.7-47.8	15.9	9.5-25.3
Others[b]	23.6	19.1-28.7	31.5	24.7-39.1	14.4	9.4-21.4
Vaccines						
CoronaVac	-	-	-	-	26.6	23.1-30.5
Astrazeneca	-	-	-	-	23.9	20.4-27.7

*[a]Psychologist, pharmacist, pharmacy assistant or technician, radiology technician, laboratory/analysis technician, nutritionist and nutrition technician, speech therapist, optician, dentist, occupational therapist, physical educator, social worker, biologist, biomedical scientist, occupational safety technician. [b]Outpatient clinics, rehabilitation service, nutrition, psychology, laboratories, pharmacy, imaging service, Central Sterile Supply Department, occupational health service, risk management, auditing, hotel management. *Confidence Interval, **Intensive Care Unit.*

Table 3. COVID-19 Prevalence Ratio adjusted for to sex, age, sector, role, type of vaccine and previous diagnosis of COVID-19.

Variables	PR*	95% CI**	*p*
Sex			>0.05
Male	0.45	0.29-0.71	
Female	0.70	0.57-0.86	
Age group			> 0.05
1st tertile (21-36 years old)	0.60	0.44-0,82	
2nd tertile (37-44 years old)	0.66	0.48-0.90	
3rd tertile (45-66 years old)	0.80	0.58-1.11	
Role			> 0.05
Nurse/nursing technician and assistant	0.75	0.58-0.96	
Physician	0.43	0.25-0.75	
Physiotherapist	0.85	0.53-1.35	
Others[a]	0.69	0.37-1.31	
Sector			> 0.05
Emergency/Inpatient/Adult ICU***	0.82	0.64-1.04	
Pediatrics/neonatology	0.68	0.41-1.72	
Surgical units	0.58	0.35-0.95	
Others[b]	0.59	0.40-0.86	
Vaccines			> 0.05
CoronaVac	0.70	0.55-0.90	
Astrazeneca	0.67	0.51-0.87	
Previously confirmed COVID-19			> 0.05
No	0.68	0.56-0.82	
Yes	0.53	0.31-0.89	

*[a]Psychologist, pharmacist, pharmacy assistant or technician, radiology technician, laboratory/analysis technician, nutritionist and nutrition technician, speech therapist, optician, dentist, occupational therapist, physical educator, social worker, biologist, biomedical scientist, occupational safety technician. [b]Outpatient clinics, rehabilitation service, nutrition, psychology, laboratories, pharmacy, imaging service, Central Sterile Supply Department, occupational health service, risk management, auditing, hotel management. *Prevalence Ratio, **Confidence Interval, ***Intensive Care Unit.*

among the unvaccinated was 51.5% (95% CI: 46.5-56.5) and among the vaccinated it was significantly lower ($p < 0.05$) at 32.1% (95% CI: 25.3-38.8). Among cases of flu syndrome occurring in workers vaccinated with CoronaVac, there was a prevalence of 26.6% of COVID-19, and among cases who received Astrazeneca, the prevalence of COVID -19 was 23.9% (Table 2).

When adjusted for these variables, it was found that, among cases of flu syndrome in professionals already vaccinated for COVID-19, there is a 33% (PR: 0.67) lower probability of having COVID-19. The CoronaVac vaccine reduces the prevalence of COVID in 30% (PR: 0.70) and Astrazeneca reduces by 33% (PR: 0.67) when compared to cases occurred in workers not yet vaccinated. A higher probability of vaccine protection against COVID-19 was observed among male professionals (PR: 0.45), among those aged between 21 and 36 years (PR: 0.60), in medical workers (PR: 0.43) and in workers of surgical units (PR: 0.58). Moreover, a previous diagnosis of COVID-19 reduced prevalence by 47% (PR: 0.53) (Table 3).

DISCUSSION

The prevalence of COVID-19 found in our study among unvaccinated professionals was higher than that reported in a previous study also conducted in southern Brazil, which presented a rate of 14.7% with data from April to June 2020.[7] In eastern Brazil, a prevalence of 42.4% of COVID-19 was identified among healthcare workers.[2] Such discrepancies may be related to the specific characteristics of the study site and the time of data collection, considering the territorial extension of Brazil,

many regions and locations presented different periods of greater and lesser spread of the disease.

There was considerable variation in the prevalence of COVID-19 among healthcare workers around the world. A similar study in Belgium identified a prevalence of COVID-19 of 49.9% (185 cases among 373 healthcare workers).[8] A study in Spain showed a prevalence of 20.1%, and another,[9] in Oman (Arabian Peninsula), a prevalence of 21.2% of COVID-19.[10] However, in Italy, a prevalence of 7.2% and 12.2% was found among symptomatic healthcare professionals or exposed to a confirmed case in the 1st wave (February 2020 to July 2020) and 2nd wave (August 2020 to January 2021), respectively.[11] When considering studies that included asymptomatic professionals, the prevalence dropped dramatically, as is the case in a study in Denmark, where the prevalence of COVID-19 in samples from asymptomatic healthcare workers with no contact with positive cases was 4.04%,[12] and in the United Kingdom and the United States of America, which was 2.7%.[3] Such differences in prevalence may be related to the working conditions of each institution and/or country, demand for care, frequency of contact with positive cases, in addition to other specific characteristics of the sample and study design that may interfere with the findings. Therefore, considering the reality of each location and identifying the specific variables related to the highest risk of contagion becomes essential to establish effective control measures.

Our finding regarding the prevalence of COVID-19 among vaccinated professionals (17.3%) was much lower than the 35.4% identified in a similar study conducted at another university hospital in southern Brazil.[13] However, a study conducted in Israel points to the same scenario of a significant reduction in COVID-19 cases after vaccination of healthcare professionals.[14] Just as the prevalence rates of COVID-19 before vaccination varied throughout the pandemic and in different countries and regions of the world, this variation was also observed even after vaccination. However, the importance of the findings lies in the significant reduction in cases regardless of the study location. In addition to this, maintaining infection control practices such use of personal protective equipment, even with adequate vaccination coverage, can also interfere with these results.

About the finding related to the higher prevalence of COVID-19 among medical workers compared to nursing team, we also found this in other studies.[10,13] Although nursing professionals present a greater risk of contamination because they have the longest contact time with patients,[15] it is known that nursing professionals demonstrate greater adherence to contamination prevention measures such as hand hygiene practice, when compared to medical workers,[16] which can positively interfere with the lower prevalence of COVID-19 in nursing professionals.

However, Gómez-Ochoa *et al*.[17] pointed to nursing as the category of healthcare workers most frequently affected by SARS-CoV-2, accounting for 48% of infected healthcare workers. It is important to highlight that nursing workers are the largest professional category in health, accounting for about 59% of healthcare workers in the world, 56% in the Americas region and approximately 70% in Brazil, so it is expected that, in absolute numbers, the contamination of nursing workers will be higher.[18, 19]

In our study, professionals in sectors that, in accordance with local institutional protocols, normally did not provide care to COVID-19 patients (such as surgical units), showed a high prevalence of COVID-19 before vaccination. Such results differ from other authors who pointed to the high prevalence of COVID-19 in sectors of care for COVID-19 patients due to a higher risk of contagion related to greater exposure.[13,20] However, institutional protocols regarding surgical procedures in symptomatic patients and non-testing in asymptomatic patients and even the possible misuse of protective equipment related to the perception of safety by professionals working in sectors that do not treat symptomatic patients may have been responsible for this outcome.

Moreover, after vaccination, we identified a significant reduction in cases of COVID-19 among professionals in sectors at greater risk of contact with contaminated patients, such as emergencies and ICUs. However, the prevalence of cases remained high among professionals in these sectors, which reinforces the importance to maintain preventive measures.

Our study did not show any significant difference in the protection provided by the use of vaccines in relation to the variables of sex, age, role, sector of activity or previous diagnosis of COVID-19, which may suggest that the protection provided by the vaccine outweighs the risk that any of these variables may confer. However, more robust studies with specific designs are needed to adequately analyze this topic.

The present study did not identify a significant difference in the protection provided by CoronaVac and Astrazeneca, unlike Toniasso *et al*.,[12] who assessed the effectiveness of both vaccines in the short term (less than three months after application). Therefore, our study, which included case data up to approximately six months after administration of the second dose of the vaccine, may suggest that, in the medium term, the effectiveness of different vaccines may become similar.

Limitations of this study include the study design that tracked and tested only symptomatic healthcare professionals. Furthermore, the study was not designed to identify the severity of infection or include data on the presence of comorbidities relevant to the SARS-CoV-2 infection process among workers. This approach limited the possibility of a better understanding of more factors related to the prevalence of COVID-19 among healthcare workers. However, the present study preserves its relevance, considering the importance of data on the medium-term impact of COVID-19 vaccination among healthcare professionals in high-complexity hospitals and findings that reinforce the impact of vaccination on communicable disease prevention.

In conclusion, our study showed a reduction in the prevalence of COVID-19 among cases of flu syndrome of

vaccinated healthcare workers when compared to cases of professionals unvaccinated for COVID-19, revealing that COVID-19 vaccination significantly reduced the chances of COVID-19 cases among healthcare workers, regardless of sex, age, sector, role, type of vaccine or previous diagnosis of COVID-19. Despite the reduction in COVID-19 cases among flu cases among professionals in sectors with a higher risk of contact with infected patients, the prevalence of cases remained high among professionals in these sectors, which reinforces the importance of maintaining complementary preventive measures, such as personal protective equipment (masks, glasses, gloves), in case of contact with patients suspected of having COVID-19. It is also worth noting that in the medium term (up to six months after the first dose), there may be no significant difference in the protection offered by CoronaVac and AstraZeneca. Thus, it reinforced the importance of COVID-19 vaccination as a practice to prevent the disease regardless of the type of vaccine available.

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AUTHORS' CONTRIBUTIONS

Karina Pinheiro Teixeira dos Reis contributed to the literature search, writing of the abstract, introduction, methodology, discussion, interpretation and description of results, preparation of tables, conclusions, review and statistics. **Mirelle de Oliveira Saes** contributed to the interpretation and description of results, explanations, review and statistics. **Ivy Bastos Ramis** contributed to the literature search, writing of the abstract, introduction, methodology, discussion, interpretation and description of results, preparation of tables, conclusions, review and statistics.

All authors approved the final version to be published and are responsible for all aspects of the work, including ensuring its version and integrity.