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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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SUMÁRIO

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Revista de Epidemiologia e Controle de Infecção

Hospital Santa Cruz

ORIGINAL ARTICLE

Epidemiological profile of individuals with HIV/Aids in a municipality in Maranhão State, Brazil, from 2017 to 2020

Perfil epidemiológico de individuos con VIH/SIDA en municipio en Maranhão, Brasil, de 2017 a 2020

Perfil epidemiológico de indivíduos com HIV/Aids em município no Maranhão, Brasil, de 2017 a 2020

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Corresponding Author:
Thiago Goncalves Araujo e Silva
goncalvesthiago48@hotmail.com

Address: Av. Dom Afonso Felipe Gregory - Main Avenue, 100. Imperatriz, MA, Brasil; CEP: 65915-240.

Thiago Goncalves Araujo e Silva[1];
Eduardo Henrique Ribeiro da Silva[1];
Francisco Jucianno Rodrigues da Silva[1];
Claudia Regina de Andrade Arrais Rosa[1];

[1] *Universidade Federal do Maranhão, Imperatriz, Maranhão, Brasil.*

ABSTRACT

Background and Objective: To understand the main forms of transmission of HIV in order to foster the containment of the transmission chain, early diagnosis and the epidemiological profile of patients. In this sense, it will enable the analysis of the epidemiological profile and the transmissibility variables of patients with HIV/Aids from the municipality of Imperatriz-MA.. **Method:** This is an observational cross-sectional study. Data collection was performed from the analysis of patients' records registered in the Center for Testing and Counseling (CTA) from 2017 to 2020. For data collection, a questionnaire with transmission variables and epidemiological characteristics of patients was used. **Results**: From January 2017 to December 2020, 211 medical records were filed. Of these, 71.6% were male, 55.5% of the participants were between 21 and 40 years, and 66.4% from Imperatriz-MA. The most prevalent type of exposure was sexual intercourse without a condom. Among the participants, 83.9% (n=177) were positive only for HIV. About 140 people with HIV had an undetectable viral load (VL) (< 50 copies/ml) after 6 months of using antiretroviral therapy, making it low transmissibility. **Conclusion:** The study was able to characterize the epidemiological profile of patients from the Specialized Assistance Service (SAE) in Imperatriz between 2017 and 2020. Despite the increase in the number of cases among women, the most affected public remains young men, from 21 to 40 years of age, with 8 to 11 years of education, single and brown. Sexual intercourse without a condom is the main type of exposure.

Keywords: *Human immunodeficiency virus. Epidemiology. Infectious disease transmission.*

RESUMEN

Justificación y Objetivo: Buscando proporcionar a la contención de la cadena de transmisión del VIH, el diagnóstico precoz y el perfil epidemiológico de los pacientes para conocer las principales formas de transmisión del VIH. En este sentido, el estudio tiene como objetivo analizar el perfil epidemiológico y las variables de transmisibilidad de los usuarios con VIH/sida del municipio de Imperatriz-MA. **Método:** Se trata de un estudio observacional de carácter

transversal, la recolección de datos fue realizada a partir del análisis de registros de usuarios registrados en el CTA en el período de 2017 a 2020. Para la recolección de datos, se utilizó un cuestionario con variables de transmisión y características epidemiológicas de los pacientes. **Resultados**: Se registraron 211 registros y enero de 2017 a diciembre de 2020. De estos, 71,6% del sexo masculino, 55,5% de los participantes tenían entre 21 y 40 años y 66,4% de Imperatriz - MA. El tipo de exposición más prevalente fue la relación sexual sin condón. Entre los participantes, 83,9% (n=177) fueron positivos solo para el VIH. Cerca de 140 personas con VIH tenían carga viral indetectable (< 50 copias/ml) después de 6 meses usando terapia antirretroviral, haciéndola de baja transmisibilidad. **Conclusión:** El público más afectado sigue siendo hombres jóvenes, de 21 a 40 años, con 8 a 11 años de educación, solteros y de piel morena. Las relaciones sexuales sin preservativo son el principal tipo de exposición.

Palabras clave: *Virus de la inmunodeficiencia humana. Epidemiología. Transmisión de enfermedad infecciosa.*

RESUMO

Justificativa e Objetivo: Conhecer as principais formas de transmissão do HIV para proporcionar a contenção da cadeia de transmissão do HIV, o diagnóstico precoce e o perfil epidemiológico dos pacientes. Nesse sentido, será possível analisar o perfil epidemiológico e as variáveis de transmissibilidade dos usuários com HIV/Aids do município de Imperatriz-MA. **Métodos:** Trata-se de um estudo observacional de caráter transversal. A coleta de dados foi realizada a partir da análise de registros de usuários cadastrados no CTA no período de 2017 a 2020. Para a coleta de dados, utilizou-se um questionário com variáveis de transmissão e características epidemiológicas dos pacientes. **Resultados**: Foram registrados 211 prontuários de janeiro de 2017 a dezembro de 2020. Destes, 71,6% do sexo masculino, 55,5% dos participantes tinham entre 21 e 40 anos e 66,4% de Imperatriz-MA. O tipo de exposição mais prevalente foi a relação sexual sem preservativo. Entre os participantes, 83,9% (n=177) foram positivos apenas para HIV. Cerca de 140 pessoas com HIV tinham carga viral indetectável (< 50 cópias/ml) após 6 meses usando terapia antirretroviral, tornando-a de baixa transmissibilidade. **Conclusões**: O estudo conseguiu caracterizar o perfil epidemiológico dos usuários de SAE em Imperatriz entre 2017 e 2020. Apesar do aumento no número de casos em mulheres, o público mais afetado continua sendo homens jovens, de 21 a 40 anos, com 8 a 11 anos de educação, solteiros e pardos. A relação sexual sem preservativo é o principal tipo de exposição.

Descritores: *Vírus da imunodeficiência humana, Epidemiologia, Transmissão de doença infecciosa.*

INTRODUCTION

The human immunodeficiency virus (HIV) is the etiologic agent that causes acquired immunodeficiency syndrome (Aids), a pathology that reduces the functions of the immune system against immunity and other opportunistic diseases. [1] The genetic material of HIV is formed by ribonucleic acid (RNA), which is transcribed into double-stranded DNA by the viral reverse transcriptase enzyme and, finally, incorporated into the host's genetic material.[2] Transmission of the HIV virus can occur through sexual, vertical, and parenteral exposure. Unprotected sexual exposure represents the main risk factor for the transmission of the virus.[3,4]

To track people infected with HIV, the Brazilian Ministry of Health has implemented the Centers for Testing and Counseling (CTA – Centro de Testagem e Aconselhamento), in order to guarantee free tests for sexually transmitted infections (STIs), including Aids.[5] The diagnosis is made through immunostatic tests such as ELISA (Enzyme-Linked Immunosorbent Assay), rapid and molecular tests, and blood samples on filter paper. Due to the user's access to Rapid Test, the detection of HIV infection can be performed in laboratory and non-laboratory environments, making it possible to expand the coverage of the diagnosis.[6]

According to data from the World Health Organization (WHO), it is estimated that in 2017 the number of people living with HIV was 37.9 million. In Brazil, the number of documented cases of HIV since the implementation of the Disease Information and Notification System (SINAN) reached the mark of 342,459 cases (2007 to 2020).[7] In Maranhão, more than 19,000 cases of Aids were reported from January 2000 to June 2020, with a detection rate in 2018 of 18.7 per 100,000 inhabitants recorded in SINAN, representing an increase of 41.7% compared to 2008.[8]

The interiorization of Aids in Brazil manifests as a discernible trend temporally and geospatially. Within the cases recorded from January 2015 to June 2020, the majority consists of males, predominantly comprised of heterosexual men, within the age range of 20 to 49 years old.[9] The epidemiological profile of SAE users in medium and small cities still requires studies, unlike national surveys that cover the population of large Brazilian capital cities. Thus, due to the socioeconomic growth of the southern region of Maranhão, associated with the demographic explosion of recent years, there has been an increase in the number of notifications due to HIV-1 infection and the spread of the epidemic to inland regions, requiring an understanding of the dynamics of the HIV infection to promote actions seeking prevention and monitoring of this disease. [10]

Comprehensive understanding of the local epidemic dynamics is paramount for the proficient formulation

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and execution of public health policies geared towards the prevention, treatment, and support of individuals living with HIV/Aids. Therefore, the present research aims to analyze the epidemiological profile and the variables of transmissibility from patients with HIV/Aids in the city of Imperatriz-MA. The information generated can contribute to the actions of the CTA and the target public to direct measures to contain the chain of transmission of HIV as well as to establish the early diagnosis of this syndrome.

METHODS

The study was characterized by being observational and cross-sectional analytical, considering that the researcher does not interfere in the exposure and outcome, which are recorded at the same time. Thus, the data was analyzed without interference from the observer. [11]

Data collected from the files of users admitted between January 2017 and December 2020 at the CTA of Imperatriz-MA who met the following criteria were included: a) age greater than or equal to 15 years; b) forms correctly completed with origin, age, gender, and date of admission to the CTA; and c) users with 2 HIV positive tests. Records of patients who, during the analysis, did not have the diagnosis confirmed through laboratory analysis and it was not possible to obtain information about the patient's clinical and epidemiological data due to incompleteness or ineligible records were excluded.

To construct the sociodemographic profile of HIV--infected users, the following variables were analyzed: age (>15 to 20 years, 21 to 40 years, 41 to 60 years, >60 years), sex (male, female), city (Imperatriz, others) years of education (none, 1 to 3, 4 to 7, 8 to 11, >12), skin color (white, brown, black, others), marital status (not married, married, widower, not informed).

The variables studied regarding the clinical and pathological history and prognoses were: recent infection with syphilis/ tuberculosis/ hepatitis b (yes, no), type of recent partners (not informed, men who have sex with men only, men who have sex with women only, women who have sex with women only, men who have sex with both men and women, men who have sex with transvestites/transsexuals), number of recent partners (1, 2, 3 to 5, 6 to 10, 11 to 20, > 20), type of exposure (sexual intercourse without a condom, mother-to-child transmission, hemophiliac/transfusion, not informed), condom use with steady partner (never, always, sometimes, not informed), condom use with casual partner (never, always, sometimes, not informed), reason for not using (trust the partner, does not like, partner does not accept, there was not enough time, under the influence of alcohol/drugs, other, not applicable), lifetime drug use (never used, drink or have drunk often, uses or has used injecting drugs, uses or has used other drugs), population group (drug user, injecting drug user, people living with HIV, men who have sex with men, sex worker, general population), VL > 1000 (yes, not), VL < 50 after 6 months (yes, no).

The data was tabulated using Microsoft Excel® software and later exported to the open-access statistical program R Studio (R Core Team, 2022®). Data analysis was performed using Pearson's Chi-Square test to compare the expected proportions between variable categories. A p value < 0.05 was considered significant.

The study was conducted obeying the ethical aspects that regulate scientific research involving human beings, published in resolution number 466/12 from the National Health Council. The study was approved by the Research Ethics Committee of the Federal University of Maranhão, with protocol CAAE 56081721.0.0000.5086 on 04/28/2022.

RESULTS

During the study period, between 2017 and 2020, 211 cases of HIV/Aids assisted at the SAE in the macroregion of Imperatriz-MA were reported. With regard to the sociodemographic profile of patients with HIV/Aids studied, our findings revealed that the sample was predominantly composed of individuals between 21 and 40 years old (55.5%, n=117) , male (71.6%, n=151), from the city of Imperatriz (66.4%, n=140), with 8 to 11 years of education (43.11%, n=91), brown skin color (64%, n=135) and not married (55%, n=116). (Table 1).

Table 1. Sociodemographic profile of patients with HIV/Aids assisted at the Specialized Assistance Service (SAE) in the macroregion of Imperatriz-MA, from January 2017 to December 2020. (n=211).

Variable	Frequency %	n
Age		
>15 to 20 years	15.6%	33
21 to 40 years	55.5%	117
41 to 60 years	24.6%	52
> 60 years	4.3%	9
Sex		
Male	71.6%	151
Female	28.4%	60
City		
Imperatriz	66.4%	140
Others	33.6¨%	71
Years of education		
None	2.8%	6
1 to 3	7.1%	15
4 to 7	31.8%	67
8 to 11	43.1%	91
> 12	15.2%	32
Skin color		
White	21.8%	46
Brown	64%	135
Black	10.9%	23
Others (yellow/indigenous)	3.3%	7
Marital status		
Not Married	55%	116
Married	35.5%	75
Widower	3.8%	8
Not informed	5.7%	12

Table 2. Distribution of transmission variables among people living with HIV assisted at the Specialized Assistance Service (SAE) in the macroregion of Imperatriz-MA, from January 2017 to December 2020. (n=211).

Variable	Frequency %	n
Recent infection with Syphilis/ Tuberculosis/ Hepatitis B		
Yes	22.3	47
No	77.7	164
Type of recent partners		
Not informed	0.5	1
Men who have sex with men only	42.1%	89
Men who have sex with women only	18.8%	39
Women who have sex with women only	29.9%	63
Men who have sex with both men and women	9.0%	19
Men who have sex with transvestites/transsexuals	4.5%	10
Number of recent partners		
1	2.8%	6
2	41.2%	87
3 to 5	15.2%	32
6 to 10	22.7%	48
11 to 20	10.9%	23
> 20	7.1%	15
Type of Exposure		
Sexual intercourse without a condom	92%	194
Mother-to-child transmission	0.9%	2
Hemophiliac/transfusion	0%	0
Not informed	7.1%	15
Condom use with steady partner		
Never	41.7%	88
Always	10.4%	22
Sometimes	43.6%	92
Not informed	4.3%	9
Condom use with casual partner		
Never	54.5%	115
Always	45.0%	95
Sometimes	0.5%	1
Not informed	0 %	0
Reason for not using condom		
Trust the partner	41.7%	88
Does not like	10.4%	22
Partner does not accept	7.1%	15
There was not enough time	11.4%	24
Under the influence of alcohol/drugs	4.7%	1
Other	14.7%	31
Not applicable	10.0%	21
Lifetime drug use		
Never used	34.6%	73
Drink or have drunk often	50.7%	107
Uses or has used injecting drugs	2.8%	6
Uses or has used other drugs (cocaine, crack)	11.8%	25
Population group		
Drug user	3.8%	8
Injecting Drug User	3.8%	8
People living with HIV	17.2%	36
Men who have sex with men	34.6%	73
Sex worker	1.9%	4
General population	38.9%	82
VL* > 1000		
Yes	67.3%	142
Not	32.7%	69
VL* < 50 after 6 months		
Yes	66.4%	140
Not	33.6%	71

Regarding clinical and pathological history and prognoses, the data indicates a higher frequency of men who have sex with men (42.1%, n=89), people without recent infection with syphilis/ tuberculosis/ hepatitis B (77.7%, n=164), who drink or have drunk often (50.7%, n=107), with 6 to 10 recent sexual partners (22.7%, n=48), who never (54.5%, n=115) or sometimes (45%, n=95) use condoms with steady partners, for trusting them (41.7%, n=88). In relation to the viral load, it was observed that 67.3% (n=140) of patients had VL>1000, and after 6 months, 66.6% had VL <50. (Table 2).

When correlating the variables among people living with HIV assisted at the SAE in the macroregion of Imperatriz-MA, it was observed that regardless of the number of sexual partners, groups that never or only occasionally use condoms predominate (p-value = 0.036). When relating viral load < 50 after ART treatment with recent STI infections, it was found that the majority of the patients without STI achieved a decline in viral load, while among those recently infected with syphilis, tuberculosis, and hepatitis B half achieved a decrease in viral load and the other half did not (p-value = 0.001). (Table 3)

Table 3. Correlation between variables among people living with HIV assisted at the Specialized Assistance Service (SAE) in the macroregion of Imperatriz-MA, from January 2017 to December 2020. (n=211).

	Sex		p-value
	Male	Female	Male
Years of education			
0 a 3 years	6	15	6
4 a 7 years	38	29	38
8 a 11 years	64	27	64
>12 years	20	12	20

	Use condom with partner Fixed			p-value
	Never	Always	Sometimes	
Number of Partners				
1	2	1	3	
2	37	9	41	0.036
3 a 5	12	4	16	
6 a 10	23	6	19	
>11	14	4	20	

	Recent infection with Syphilis/ Tuberculosis/ Hepatitis B		p-value
	Yes	No	
Viral load < 50 ART treatment			
Yes	23	117	0.001
No	24	47	

DISCUSSION

After analyzing the sociodemographic variables, an increase in cases was observed in the southern region of Maranhão, due to the rapid economic growth resulting from the installation of agricultural companies and the offer of formal job vacancies in the region.[13] When addressing the predominance of gender, there was a gre-

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ater number of male patients (71.6%). This finding reaffirms the prevalence of 7HIV/Aids cases among men in the country between 2017-2020, in which more than 70% of cases occurred in men. The data is similar to the study carried out at the reference hospital for the treatment of HIV/Aids in Goiânia, Goiás, where (56.6%) of the patients were men.[13]

Although, an increase in the number of cases among females was noted over time. In Brazil, from 2008 to 2020, there was an increase in the participation of women in cases of HIV. With that, monitoring the historical evolution, 688,348 cases of HIV were notified in men and 356,885 in women. Over time, the ratio between the sexes has been progressively decreasing. In 1985, the ratio was 15 cases in men to one case in women. Currently, the ratio is 2.4 to one.[7]

Since 2013, there has been a decrease in the number of Aids cases among women and men. In 2017, the proportion of Aids cases reported on SINAN by gender was male 2.3:1 female. In Imperatriz, in 2014, the proportion of cases by sex was 1:1, and in 2020 the ratio was male 2.3:1 female. Data that confirms other studies, where the centralization of the number of cases is observed in areas that suffer population explosion and with high demographic density, due to the intense migration of individuals with variable health conditions that need tracking, diagnosis, and treatment in more urbanized regions.[15]

As for the incidence of cases of HIV/Aids reported, in the Northeast region cases jumped from 3,190 in 2018 to 3,322 in 2019. In Imperatriz, there was a drop in cases compared to previous years. With the COVID-19 pandemic period, the number of confirmed cases in the country reduced by 67.34% (2019: 26,141 cases in men; 2020: 8,434 cases in men).[16] This drop reflects the possible underreporting of cases, due to the social isolation proposed during the COVID-19 pandemic period and also the reallocation of health professionals to other sectors to fight the new virus. Thus, a progressive increase in the number of cases between 2020 and 2022 is expected, leading to consequences in the promotion, prevention, and care of patients with HIV.[17]

In our findings, it was observed that the primary age group living with HIV/Aids in Imperatriz is between 21 and 40 years old, aligning with the epidemiological profile in Brazil.[9] As for the level of education, participants with complete secondary education, followed by those who completed elementary school, predominated in this study, with 43% and 31% respectively. This data reaffirms the information collected for cases of HIV/Aids in Brazil between 2013 and 2017. In this period, the percentage of HIV-positive patients who attended high school was 38.4%, and elementary school 37.5%.[15]

It was also verified that the highest percentage of the population self-declared brown 64.0% (135), followed by white 21.8% (46), and black 10.9%. This data is in accordance with the national scenario. According to the Ministry of Health, between 2013-2017, cases of HIV/Aids predominated among white (44%) and brown (43.5%) ethnic groups. Overall, the division of cases is in line with the ethnic prevalence of the country. According to the Brazilian Institute of Geography and Statistics (IBGE), in the period from 2012 to 2019, 46.8% of Brazilians self-declared to be brown, 42.7% white, 9.4% black and 1.1% yellow or indigenous.[7]

Research data reveals that 34.6% of male patients claim to have sex with another man. According to another study, it is noted that the number of cases among young men who have sex with men (MSM) increased by 140% between 2009 and 2016. Considering general data, the prevalence of MSM with HIV jumped from 12.1% to 18. 4% - 1.5 times higher.[4]

According to the Ministry of Health, it is possible to notice a gradual increase in HIV/Aids infections among MSM in the last decade, which jumped from 35.6% in 2006 to 47.3% in 2016, an increase of 32.9%. The growing prevalence of AIDS and the number of people infected with HIV among MSM reflects the moral reaction to sexual practices. However, it is necessary to consider that in addition to social and programmatic issues, individual and subjective decisions contribute to the conversion of social groups that are more vulnerable to HIV.[17]

As for the population group, the proportion of heterosexual patients with HIV/Aids is on average 38% of the cases. In Imperatriz, the cases reported between 2016-2020 among heterosexuals correspond to 56% of all cases reported. [15] It is important to emphasize that, in this research, the number of MSM, homosexuals and bisexuals may be underestimated, as the answers given by patients may not represent their real sexual inclination. And conversely, the prevalence of heterosexuals may be overestimated. Since the categorization of homosexual and bisexual is influenced by ethical and cultural issues, the population tends to highlight their heterosexual relationships as a form of social acceptance.[18]

Regarding the reasons for not using condoms, the population studied claims to dismiss prevention measures during sexual practices with occasional or steady partners, even though they recognize the importance of prevention. In this study, it was observed that 17% of patients reported trusting their partner and therefore never using condoms in sexual intercourse with occasional partners, despite of knowing their importance for preventing STI. In this sense, it is necessary to integrate and offer education about HIV/Aids to promote the continuous use of prevention methods.[19]

Observational studies with serodiscordant couples reveal that antiretroviral treatment in patients with HIV-1 decreases sexual transmission of the virus. Early therapy reduces the risk of HIV-1 infections by 96%. In this research, it was observed that 32.7% of those infected started early antiretroviral therapy with expressive results in the reduction of the viral load and, consequently, in the viral transmission chain. Thus, the Ministry of Health establishes that all infected people who are not yet receiving ART should receive ART, regardless of their CD4+ count.[20]

It is observed that cases of HIV/Aids in the country began in the social classes with higher education, with considerable expansion to the classes with lower education.[12] The study showed significance (p-value < 0.05) in the proportion of participants with low education, in

which 43.1% have only completed elementary school. In females, it is observed that the lower the education level, the higher the risk of exposure, similar to data from the Southeast and Midwest regions of Brazil. Thus, this data reflects the patterns of involvement related to knowledge and education deficiency.[21]

Statistically proven, individuals with recent infections of syphilis, tuberculosis, or hepatitis B show positive responses to treatment, achieving parity with those without recent infection regarding undetectable viral load after 6 months of ART. This observation is substantiated by a study conducted in Belo Horizonte, the capital of the state of Minas Gerais, Brazil. The study found that at the end of 12 months of ART, only 6.8% of individuals co-infected with syphilis and HIV had a detectable viral load.[22]

The limitation of the present study is related to the method used in the collection of data, which was obtained through medical records, performed by health professionals and presented with incomplete filling. The lack of records such as symptoms, cause of death, and laboratory follow-up data, among others, significantly impairs the description of the epidemiological and clinical pattern of the study.

The study characterized the epidemiological profile of SAE users in Imperatriz between 2017 and 2020. Despite the increase in the number of cases among women, the most affected public remains young men, from 21 to 40 years, with 8 to 11 years of education, single and brown. Sexual intercourse without a condom is the main type of exposure. In this sense, it is necessary to develop public health policies aimed at this community to adopt relevant and effective actions for the promotion, prevention, and restoration of health, seeking to promote condom use and health education regarding HIV/AIDS infection, focusing in their sociodemographic and clinical characteristics and social motivators.

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AUTHORS' CONTRIBUTIONS

Thiago Goncalves Araujo e Silva contributed to the interpretation of data and writing of the article. **Francisco Jucianno Rodrigues da Silva** and **Eduardo Henrique Ribeiro da Silva** contributed to the conception and design of the study, data analysis and critical review of the manuscript. **Claudia Regina de Andrade Arrais Rosa** contributed to the design of the project and relevant critical review of the intellectual content.

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ORIGINAL ARTICLE

Epidemiological profile of accidents involving venomous animals in Maranhão from 2012 to 2021

Perfil epidemiológico de acidentes envolvendo animais peçonhentos no Maranhão no período de 2012 a 2021

Perfil epidemiológico de los accidentes con animales venenosos en Maranhão de 2012 a 2021

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Corresponding Author:
Letícia Lima da Silva
ticia.limasilva2@gmail.com

Address: Av. Dom Jaime de Barros Câmara, 90 - Planalto, São Bernardo do Campo - SP, 09895-400

Letícia Lima da Silva[1];
Fernanda Carvalho Camargos Vieira[1];
Laís Gomes Ferreira Rosa[2];
Rita de Cassia da Silva Oliveira[3];
Sávia Lorena Costa[4];
Guilherme de Andrade Ruela[5];

[1] *Universidade Nove de Julho, São Bernardo do Campo, São Paulo, Brazil*
[2] *Centro Universitário de Várzea Grande, Várzea Grande, Mato Grosso, Brazil*
[3] *Universidade Nilton Lins, Manaus, Amazonas, Brazil*
[4] *Centro Universitário CESMAC, Maceió, Alagoas, Brazil*
[5] *Universidade Federal de Juiz de Fora, Governador Valadares, Minas Gerais, Brazil*

ABSTRACT

Background and Objectives: the second greatest cause of human poisoning in Brazil is caused by venomous animals. Thus, this study aimed to analyze clinical and sociodemographic data, in order to outline the epidemiological profile of accidents involving venomous animals in Maranhão. **Methods:** this is an ecological study with a quantitative approach, carried out from data collection by the Notifiable Diseases Information System (SINAN) of notifications of accidents by venomous animals that occurred in the state of Maranhão from 2012 to 2021. **Results:** of the 34,808 cases reported, it was found that the highest incidence occurred in 2019 and, in general, January is the month in which most accidents are recorded. When analyzing the sociodemographic profile, it is noted that the majority of victims are represented by male individuals, between 20-39 years old, with an unidentified level of education. In the case of clinical and epidemiological criteria, it was evident that snakes of the genus *Bothrops* are responsible for the highest incidence, with most cases involving venomous animals occurring within 1-3 hours after the bite. Among the cases identified, 63% were described as mild and 82% progressed to cure. **Conclusion:** the epidemiological profile described in the study can be used by health agents to plan preventive measures in Primary Health Care, and knowing the profile of victims is essential to prevent and promote quality care.

Keywords: *Scorpion. Snakes. Epidemiology.*

RESUMO

Justificativa e Objetivos: a segunda maior causa de envenenamento humano no Brasil é ocasionada por animais peçonhentos. Dessa forma, este estudo visou analisar dados clínicos e sociodemográficos, a fim de traçar o perfil epidemiológico dos acidentes envolvendo animais peçonhentos no Maranhão. **Métodos:** trata-se de estudo

ecológico de abordagem quantitativa, realizado a partir da coleta de dados pelo Sistema de Informações de Agravos de Notificação (SINAN) de acidentes por animais peçonhentos ocorridos no estado do Maranhão no período de 2012 a 2021. **Resultados:** dos 34.808 casos notificados, constatou-se que a maior incidência ocorreu no ano de 2019 e, em geral, janeiro é o mês em que mais se registram acidentes. Ao analisar o perfil sociodemográfico, nota-se que a maior parte das vítimas é representada por indivíduos do sexo masculino, entre 20 e 39 anos, com grau de escolaridade não identificado. Tratando-se de critérios clínicos e epidemiológicos, evidenciou-se que as serpentes do gênero *Bothrops* são as responsáveis pela maior incidência, sendo que a maior parte dos atendimentos envolvendo animais peçonhentos ocorreu no intervalo de 1-3 horas após a picada. Entre os casos identificados, 63% foram descritos como leve e 82% evoluíram para a cura. **Conclusão:** o perfil epidemiológico descrito no estudo pode ser utilizado por agentes de saúde para o planejamento de medidas preventivas na Atenção Primária à Saúde, e conhecer o perfil das vítimas é essencial para prevenir e promover uma assistência de qualidade.

Descritores: *Escorpião. Serpentes. Epidemiologia.*

RESUMEN

Justificación y Objetivos: la segunda causa de envenenamiento humano en Brasil es causada por animales venenosos. Así, este estudio tuvo como objetivo analizar datos clínicos y sociodemográficos, con el fin de delinear el perfil epidemiológico de los accidentes con animales venenosos en Maranhão. **Métodos**: se trata de un estudio ecológico con abordaje cuantitativo, realizado a partir de la recolección de datos por el Sistema de Información de Enfermedades de Declaración Obligatoria (SINAN) de relatos de accidentes por animales ponzoñosos ocurridos en el estado de Maranhão entre 2012 y 2021. **Resultados**: de los 34.808 casos reportados, se encontró que la mayor incidencia ocurrió en 2019 y, en general, enero es el mes en el que se registran más accidentes. Al analizar el perfil sociodemográfico, se observa que la mayoría de las víctimas están representadas por personas del sexo masculino, entre 20-39 años, y con nivel de escolaridad no identificado. En el caso de los criterios clínicos y epidemiológicos, se evidenció que las serpientes del género *Bothrops* son las responsables de la mayor incidencia, y la mayoría de los casos que involucran animales venenosos ocurren entre 1 y 3 horas después de la mordedura. Entre los casos identificados, el 63% fueron descritos como leves y el 82% progresó hacia la curación. **Conclusión:** el perfil epidemiológico descrito en el estudio puede ser utilizado por los agentes de salud para planificar medidas preventivas en la atención básica de salud, y conocer el perfil de las víctimas es fundamental para prevenir y promover una atención de calidad.

Palabras Clave: *Escorpión. Serpientes. Epidemiología.*

INTRODUCTION

Venomous animals are recognized by those who produce venom and are able to inject it, such as snakes, scorpions, bees and beetles. Snake accidents are part of the list of neglected tropical diseases and represent a public health problem, recognized by the World Health Organization (WHO) as belonging to the list of neglected tropical diseases, a fact that even motivated the WHO to modify the strategic tools to eliminate neglected tropical diseases, with the aim of overcoming this situation by 2030.[1]

In Brazil, accidents involving venomous animals have become a problem for public health and are responsible for clinical emergencies, which require immediate assistance due to pathophysiological changes.[2] On average, 200 deaths are recorded annually for every 100,000 cases, making it the second largest cause of poisoning in humans.[1-3] For this reason, the diagnosis of accidents must be reported by clinical-epidemiological emissions by filling out the Venomous Animal Accident Investigation Form in the Notifiable Diseases Information System (SINAN - *Sistema de Informação de Agravos de Notificação*).[4]

This scenario has been justified by climate and environmental changes caused by disorderly urban growth, which has been causing an imbalance in these animals' natural habitat. Thus, these factors are conditions for venomous animals to migrate from the wild to rural and urban areas in search of food and to attack as a form of defense. As a result, there is an increasing number of peri- and intra-domestic accidents, in addition to an increase in occupational risks of workers in the agricultural sector.[4,5]

The epidemiology of these accidents in northeastern Brazil, including the state of Maranhão, is still poorly understood,[6] especially in the context of these environmental changes in recent years. Furthermore, although there are studies that gather epidemiological data on these complications in Brazil, there are few studies in the literature that specifically deal with the state of Maranhão.

Thus, considering that accidents caused by venomous animals are considered neglected in the country, it is necessary to know the epidemiological profile to conduct prevention policies and guidelines for these risk groups that affect vulnerable, low-income individuals, workers, rural residents, peripheral communities in rural and urban areas, flows of places that bring human beings and the natural habitat together.[3,7] In this context, this study aimed to outline the epidemiological profile of accidents caused by venomous animals in the state of Maranhão from 2012 to 2021.

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METHODS

This is an ecological epidemiological study. Data was collected on cases reported to victims of accidents caused by venomous animals in the state of Maranhão between January 2012 and December 2021. The state has a total territorial area of 329,651,496 km² and has an approximate population of 6,775,152 inhabitants (Figure 1).[8]

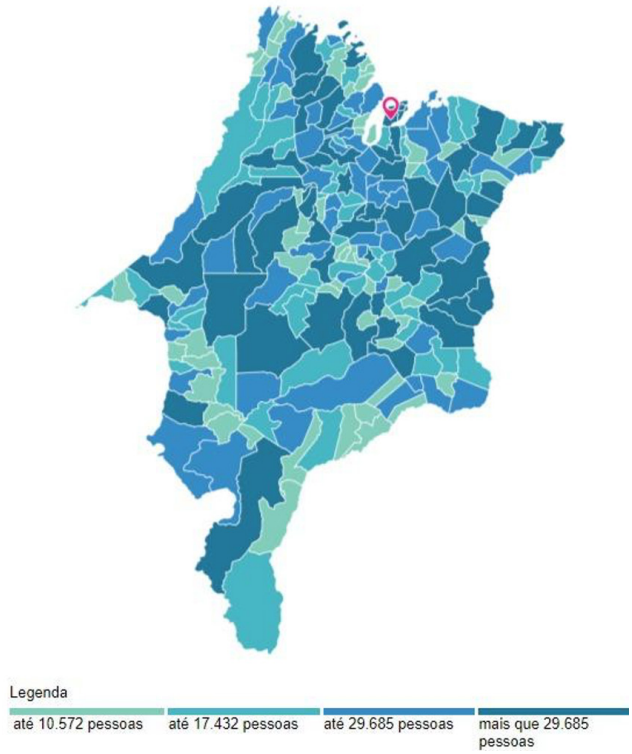

Figure 1. Population map of the state of Maranhão
Source: Brazilian Institute of Research and Statistics, 2022.

Information regarding patients' epidemiological profile was obtained through SINAN, made available by the Ministry of Health. Data was obtained from notification forms filled out by the local health service and stored in the TABNET program, public domain system provided by the Brazilian Health System Information Technology Department (DATASUS - *Departamento de Informática do Sistema Único de Saúde*), accessed on January 18, 2023.

After data collection, sociodemographic variables (sex, age group, education, race and period of gestation) and clinical-epidemiological variables (number of reported accidents caused by venomous animals, accident seasonality through monthly analysis, cause of accident, scorpion/snake/spider genus, final classification of the case, case evolution and time between bite and assistance).

To analyze the variables, stratified descriptive statistical analyzes with a quantitative approach were carried out in the form of proportions establishing the frequency of variables using Microsoft Excel Professional Plus 2021.

Incidence rates were calculated based on information accessed on the TABNET platform, to obtain the number of cases, and on the Brazilian Institute of Geography and Statistics (IBGE - *Instituto Brasileiro de Geografia e Estatística*) portal, to obtain the number of the resident population. The TABWIN program was used to perform this calculation.

As this work is carried out using information derived from secondary data sources in the public domain and without the possibility of identifying individuals, there is no need to submit a project to a Research Ethics Committee (REC), in accordance with Resolution 510/16 of the Brazilian National Health Council (2016).

RESULTS

In the state of Maranhão, a total of 34,808 accidents involving venomous animals were reported from 2012 to 2021. From data tabulation, the highest incidences were observed in 2019 (n=5,274; 74.45/100 thousand inhabitants), 2021 (n=5,188; 72.49/100 thousand inhabitants) and 2020 (n=4,815; 67.62/100 thousand inhabitants). The lowest incidence was recorded in 2012 (n=1,981; 29.42/100 thousand inhabitants) (Figure 2).

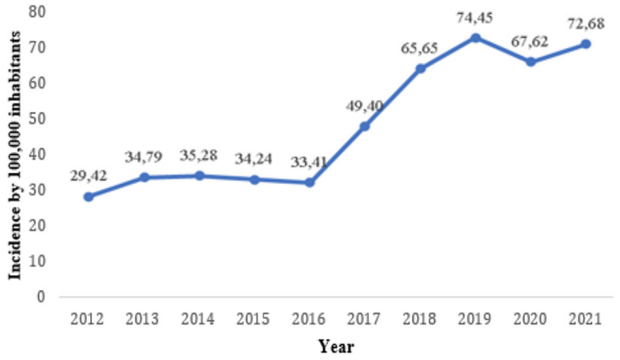

Figure 2. Incidence of accidents caused by venomous animals per 100 thousand inhabitants from 2012-2021, n= 34,808.
Source: adapted from SINAN.

It was observed that accidents occurred more frequently in January (n=3,563; 10.24%), February (n=3,396; 9.76%) and May (n=3,332; 9.57%), and less frequently in October (n=2,265; 6.51%) (Figure 3).

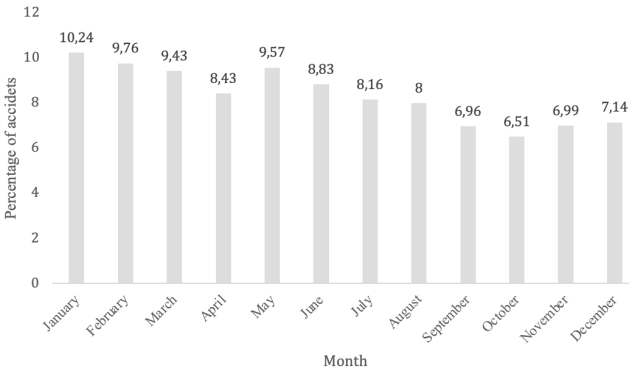

Figure 3. Seasonality of accidents caused by venomous animals registered in the state of Maranhão from 2012-2021, n=34,808.
Source: adapted from SINAN.

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Regarding the sociodemographic profile, it was shown that 66.65% (n=23,199) of victims were male, while 33.34% (n=11,605) were female. Most cases occurred in the 20-39 age group (n=12,260; 35.22%), in brown people (n=26,553; 76.28%), whose education was up to elementary school (n =17,126; 49.20%). In relation to pregnancy, the majority of occurrences do not apply (n=26,737; 76.81%) due to predominance of males. However, among the accidents in which victims were pregnant (n=287), the 2nd trimester was the period with the highest number of cases (n=104; 36.23%) (Table 1).

Table 1. Sociodemographic profile of victims of accidents caused by venomous animals in the state of Maranhão, 2012-2021, n=34,808.

Variables	N = 34,808	%
Sex		
Male	23,199	66.65
Female	11,605	33.34
Ignored	4	0.01
Age group		
<1 year	560	1.61%
1 to 4	1,242	3.57%
5 to 9	2,036	5.85%
10 to 14	2,695	7.74%
15-19	3,293	9.46%
20-39	12,260	35.22%
40-59	8,804	25.29%
60-64	1,475	4.24%
65-69	1,016	2.92%
70-79	1,086	3.12%
80 and +	334	0.96%
Ignored/blank	7	0.02%
Education		
Not educated	2,579	7.41%
Elementary school	17,126	49.20%
High school	3,263	9.37%
University education	396	1.14%
Not applicable	2,513	7.22%
Ignored/blank	8,931	25.66%
Race		
White	2,732	7.85%
Black	2,691	7.73%
Yellow	448	1.29%
Brown	26,553	76.28%
Indigenous	1,372	3.94%
Ignored/blank	1,012	2.91%
Gestation		
1st trimester	56	0.16%
2nd trimester	104	0.30%
3rd trimester	64	0.18%
Gestational age ignored	63	0.18%
No	7,129	20.48%
Not applicable	26,737	76.81%
Ignored/blank	655	1.88%

Source: adapted from SINAN.

The analysis of clinical and epidemiological characteristics revealed a higher incidence of accidents involving snakes (48.96%), while the highest fatality rate was for incidents involving spiders, compared to other reported etiological agents. As for the final classification, of the 34,808 cases, 22,270 were classified as mild. Regarding the outcome, 82.02% were cured. The most common time between the incident and the most common treatment was in the range of 1 to 3 hours (34.04%).[7]

Table 2. Clinical and epidemiological characteristics of accidents caused by venomous animals in the state of Maranhão from 2012 to 2021.

Accident etiology	Notifications	%	Deaths	Lethality
Scorpion	12,686	36.44%	45	0.30%
Snake	17,044	48.96%	113	0.60%
Spider	1,623	4.66%	14	0.80%
Bee	1,345	3.86%	10	0.70%
Caterpillar	699	2%	3	0.42%
Others	1,130	3.24%	4	0.35%
Ignored/blank	311	0.89%	3	0.96%
Caused by snake	**Notifications**	**%**	**Deaths**	**Lethality**
Bothrops spp.	11,274	66.14%	51	0.45%
Crotalus spp.	3,900	22.88%	57	1.46%
Micrurus sp.	139	0.81%	-	-
Lachesis sp.	89	0.52%	-	-
Non-venomous	569	3.33%	1	0.17%
Ignored/blank	1,073	6.29%	4	0.44%
Spider genus	**Notifications**	**%**	**Deaths**	**Lethality**
Phoneutria	107	6.59%	-	-
Loxosceles	452	27.84%	6	1.32%
Latrodectus	20	1.23%	1	5%
Another species	447	27.54%	3	0.67%
Ignored/blank	597	36.78%	4	0.67%
Final classification	**Notifications**	**%**	**Deaths**	**Lethality**
Light	22,270	63.97%	78	0.35%
Moderate	8,549	24.56%	48	0.56%
Serious	1,114	3.20%	57	5.11%
Ignored/blank	2,875	8.20%	9	0.31%
Case evolution	**Notifications**	**%**	**Deaths**	**Lethality**
Cure	28,560	82.05%	-	-
Death	192	0.55%	192	100%
Death from other causes	5	0.01%	-	-
Ignored/blank	6,051	17.38%	-	-
Time between bite and assistance	**Notifications**	**%**	**Deaths**	**Lethality**
0-1 hour	10,581	30.39%	48	0.45%
1-3 hours	11,976	34.40%	59	0.49%
3-6 hours	5,099	14.64%	25	0.20%
6-12 hours	1,842	5.29%	17	0.92%
12-24 hours	1,408	4.04%	17	1.20%
More than 24 hours	1,511	4.34%	14	0.92%
Ignored/blank	2,391	6.86%	12	0.50%

Source: adapted from SINAN.

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From an analysis focused on the clinical-epidemiological profile (Table 2), it was noted that the main causes of injuries are snakes (48.92%) and scorpions (36.4%). On the other hand, accidents caused by spiders (4.66%) and bees (3.86%), although they occurred in smaller numbers, were the most lethal.

Regarding snake genus, an important factor for choosing the specific antidote, it is noted that there is a preponderance of the genus *Bothrops* (*jararaca, jararacuçu*), with 66.14% of the total cases, followed by snakes of the genus *Crotalus* (rattlesnake), with 22.88%. In terms of lethality, accidents caused by rattlesnakes were the most fatal.

Of the injuries caused by spiders, there is a great deal of misinformation regarding genus, since 36.78% of incidents did not record this information. Despite this, from the analysis of available data, it appears that the genus *Loxosceles* had the highest number of cases (n=452) and the highest fatality rate (1.32%).

In the case of the final classification of cases, approximately 63% of accidents caused by venomous animals were considered mild, 24.56% moderate, 8.20% ignored/blank, and 3.20% severe. However, the lethality of severe cases was 5.11%, resulting in 57 deaths out of the 1,114 registered, while in cases identified as mild and moderate, fatality rates were, respectively, 0.35% and 0.56%. As for case evolution, the majority of accidents resulted in a cure, 82.05% (n=28,560), and only 0.55% of accidents resulted in death (n=192).

The lack of adequate understanding to classify accidents, combined with the discrepancy in case developments, reveals the gap in knowledge that exists in relation to incidents caused by venomous animals. Additionally, it denounces the deficiencies inherent to the Brazilian health system regarding the systematic and reliable data recording, since the progression of events from mild to moderate severity to fatal outcomes is not justified due to the lack of logical cohesion in this context. This problem corroborates other studies, which suggest difficulties in obtaining information about patients' clinical evolution.

When analyzing the time elapsed between bite and treatment, it is possible to see that, in cases treated within 12-24 hours after the bite, the fatality rate was 1.20%. On the other hand, cases in which care was provided within the first 6 hours after the bite achieved the highest cure rates.

DISCUSSION

Accidents caused by venomous animals, in general, are influenced by several variables, such as diversity and specificity of fauna, flora and regional ecosystem, local socioeconomic activities, degree of human contact with animals' natural habitat, the level of aversion to them and other factors that fluctuate over time, such as rainfall levels and temperature.[5,9,10]

It is possible to observe that, throughout the Brazilian territory, the number of accidents caused by venomous animals has been growing too much, including in large urban centers. This fact is due to imbalance of fauna as a result of the advance of deforestation and disorderly urban growth, generating an overlap between these animals' natural habitat and urban occupations, making peri- and intra-household accidents increasingly common. Here accidents with snakes stand out, and in Brazil the term "urbanization of snakebite" has already been adopted.".[11,12]

In relation to accident seasonality, it is possible to verify that January, February and May have the highest number of reported accidents from 2012 to 2021. This data highlights the relationship between accidents and rainfall rates and temperature variations during the year, relating to the season, with high rainfall and hot weather, characteristic of summer, which creates an environment conducive to these animals' reproduction. Thus, this seasonal pattern is also repeated in other studies.[5,10,13]

Thus, in the period under analysis, it was observed that there was a progressive increase over time, in line with studies previously carried out in other states.[11-14] This increase may be due to improvements in the notification system, in order to show increasingly reliable values, or be, in fact, a representation of the growing number of cases.[13]

Furthermore, it is possible to relate the drop in notifications in 2020 to the COVID-19 pandemic, since quarantine and the suspension of several activities occurred during this period, reducing the exposure of the population at occupational risk to this type of injury, or just by undernotification. However, it is worth noting that, despite the decrease in cases during the pandemic period, the numbers remained double when compared to some previous years, highlighting the epidemiological importance of these diseases.

The relationship between accidents and the development of work activities related to agriculture, construction and livestock farming justifies the majority of victims being male (n=23,199; 66.65%), at an economically active age of 20-39 years old and self-declared browns, whose level of education was ignored. This profile is characteristic and is repeated in the vast majority of studies,[5,11–18] as men tend to be more involved with activities in this sector of the economy, making them more vulnerable to accidents with venomous animals, with emphasis on snakebites and scorpionism, more common in the context of occupational risk, in addition to the risk arising from subsistence agriculture in rural areas.[10,12]

Due to possible complications caused by the venom, such as hemorrhage, uterine contraction, threat of abortion, decreased fetal movements and, in more serious cases, even fetal and maternal death,[19,20] the gestational period was used as an analysis criterion. In this study, most occurrences do not apply, as illnesses were more common. However, in cases where there was positivity for pregnancy, the 2nd trimester was the period with the highest number of cases.

Of the 34,808 cases, the most common symptoms were pain, edema and bruising, without complications such as shock, hemorrhage and anuria, since 63.97% of accidents were classified as mild. Bites usually occur on extremities of the body, such as hands, arms, legs and feet.[20]

Snake bites were included in the list of Neglected

Tropical Diseases (NTDs) in category A, in 2017, by the WHO, signaling their importance for public health.[21] In Maranhão, snakebites had the highest incidence among those caused by venomous animals, totaling 48.96% of cases. This finding reveals an increase in the number of snakebites when compared to research carried out in the same state in previous years.[5] Furthermore, studies[14,20] corroborate that snakebite accidents predominate in the Northeast, since 43% of species of medical importance in Brazil inhabit this region, and this is due to the better adaptation of these species in humid environments. Of the 25 species concentrated in the Northeast, 24 are found in Maranhão, and may be from the genera *Bothrops, Micrurus*, *Crotalus* or *Lachesis*.[7]

Among snakebites, bites by snakes of the genus *Bothrops*, belonging to the family *Viperidae*, have a higher incidence in Brazil, especially in rural areas, where human interaction with the environment is greater.[22,23] In Maranhão, similarities were observed, since the diseases caused by snakes *jararaca* and *jararacuçu*, of the genus *Bothrops*, had a higher incidence, followed by the coral snake, of the genus *Micrurus*, belonging to the family *Elapidae*, considered the most lethal.

In second place are accidents caused by scorpion stings, corresponding to 36.44% of cases. Scorpionism has a high incidence throughout Brazil, and is considered a public health problem, especially in the Northeast region[23]. However, in contrast to snakebites, scorpionism is prevalent in urban environments.[23,25]

There are more than 2,600 species of scorpions in the world, but in South America, mainly in Brazil, the genus *Tityus* stands out in the medical field.[25] Furthermore, in northern and northeastern Brazil, there is a favorable climate for the proliferation of this genus. Among the species, T. *serrulatus* stands out, known as the yellow scorpion, widely distributed throughout the Brazilian territory due to its easy adaptation in urban environments and parthenogenetic reproduction, characteristics that favor its rapid dissemination in different areas. There are also studies that associate a higher lethality rate with the species T. *obscuras*, common in hot and humid regions, such as the Amazon regions, the place with the highest occurrence of lethal accidents involving the species. Concern about the severity of accidents caused by this species of scorpion occurs due to the neurotoxic venom it inoculates, whose response to treatment is not as good.[11,26] Regarding symptoms, local pain is present in all cases, and other symptoms can vary according to severity, from hyperemia and sweating to systemic manifestations and multiple organ failure, with the pediatric age group being the most vulnerable.[24,26]

Accidents caused by spiders, although not the most common, were the most fatal, and this fact can be explained by the lack of adequate treatment due to the failure to identify the causative agent. Identification of a spider's gender is of great importance for case evolution and victim prognosis. Among the recorded genera, a greater number of accidents caused by the known "brown spiders", of the genus *Loxoceles*, were observed. It is important to highlight that, despite their non-aggressive tendency, when subjected to compression, they tend to adopt a defensive attitude. Furthermore, it is worth highlighting the color of these arachnids, which can make identification difficult, especially when they are found in clothing, waste and tree trunks in rural environments.[20]

Another genus of spiders reported is *Phoneutria*, popularly known as "armor spiders". These, as the name suggests, have more aggressive defense behavior and arm themselves when coming into contact with victims. They are nocturnal, which increases the risk of accidents in areas close to construction and debris at night when they go hunting.[20]

Furthermore, the time elapsed between the animal being bitten and the victim being treated is a very important point to be assessed, as it directly affects case evolution. In this context, it is considered early when done in an interval between bite and treatment <6 hours and late when >6 hours.[27] The present study found that the highest fatality rate occurred in treatments carried out within 12-24 hours, a finding consistent with the literature that predicts less success in treatment when it is carried out 6 hours after the accident,[20,27] highlighting the need for develop strategies for timely care.

In relation to case evolution, 82.05% progressed to cure, while only 0.55% of accidents resulted in death. This finding corroborates the results found in other studies.[18,20] These numbers may be related to time between bite and assistance in Maranhão, since in 79.43% (n=27,656) of cases treatment occurred between 0-6 hours after the accident, or due to the final classification of cases, in which 88.53% (n=30,819) were mild or moderate, while only 3.2% were serious.

The epidemiological profile of cases of accidents caused by venomous animals in the state of Maranhão from 2012 to 2021 showed a predominance of individuals whose education was unknown, aged between 20 and 39 years, male and brown. It was also possible to determine that accidents occurred more frequently in months with hotter and more humid climates, in addition to the increase in 2019, 2020 and 2021.

Human interaction in the environment is increasing the number of cases, whether due to the increase in global temperature or the invasion of preserved environments leading to greater contact between humans and venomous animals. Therefore, the growth analyzed in recent years leads to the need for measures to prevent and promote health, in addition to environmental preservation.

Therefore, it is important to highlight the relevance of this study for assessing the epidemiological profile that, through quantitative analysis, allowed monitoring the number of cases and variation due to socioeconomic characteristics, contributing to the development of public strategies to reduce morbidity and mortality from accidents caused by venomous animals.

It is worth highlighting that health depends on other factors and sectors, such as education and infrastructure. Therefore, the data presented here can be used by health agents to plan and organize prevention measures in Pri-

mary Health Care, with educating the population about risk factors. Alerting the population about the danger of accidents with venomous animals in land with a large accumulation of rubble and garbage, together with recommending the use of protective equipment, such as boots and gloves, by rural workers, are actions that can significantly contribute to the reduction of cases of injuries involving these animals.

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AUTHORS' CONTRIBUTIONS

Letícia Lima da Silva, Fernanda Carvalho Camargos Vieira and Rita de Cassia da Silva Oliveira contributed to article conception, design and manuscript writing. **Sávia Lorena Costa and Laís Gomes Ferreira Rosa** contributed to data analysis and interpretation and manuscript writing. **Guilherme de Andrade Ruela** contributed to the planning and design of the article, review and final approval of the article.

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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ORIGINAL ARTICLE

Clinical characteristics, epidemiology, and mortality of patients receiving antifungal therapy at a university hospital of the Triângulo Mineiro, Brazil

Aspectos clínicos, epidemiológicos e mortalidade de pacientes em uso de terapia antifúngica em um hospital universitário do Triângulo Mineiro, Brasil

Aspectos clínicos, epidemiológicos y mortalidad de pacientes en uso de terapia antifúngica en un hospital universitario del Triângulo Mineiro, BrasiL

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Corresponding Author:
Reginaldo dos Santos Pedroso
rpedroso@ufu.br

Address: Avenida Amazonas s/nº - Bloco 4k - Sala 321, Umuarama,38400902 - Uberlândia, MG - Brasil. Tel/Fax: (34) 32258459.

Flávia Maria Pinto Monteiro Antonieti[1];
Reginaldo dos Santos Pedroso[1];
Maria Ângela Ribeiro[1];
Lúcio Borges de Araújo[1];
Denise Von Dolinger de Brito Roder[1];

[1] *Universidade Federal de Uberlândia, Minas Gerais, Brasil.*

ABSTRACT

Background and Objectives: Invasive fungal infections are associated with high morbidity and mortality in patients admitted to hospital, including those receiving appropriate therapy. The aim of this study was to evaluate the use of prophylactic and preemptive antifungal therapy; clinical and epidemiological features; and mortality of patients admitted to an infectious disease ward of a public high complexity hospital in Uberlandia, Minas Gerais, Brazil. **Methods:** This is a retrospective study carried out in the infectious diseases ward of a public university hospital in Brazil. Data from patients hospitalized in 2019 and 2020 who received azole antifungals (fluconazole, itraconazole, or voriconazole), echinocandin (anidulafungin), and polyene (amphotericin B) were collected from medical records. **Results:** During the study period, 111 patients received one or more antifungal agent. The length of hospital stays of patients (29.35 days; p=0.0252), mean number of days of antibacterial drug use (23.5 days; p=0.0164), a diagnosis of AIDS (p=0.0397), mechanical ventilation (MV) (p<0.001), and presence of a nasoenteral tube (p<0.01) were variables that were associated with death. Fungal infection was confirmed in 79 (71.2%) patients who used antifungal drugs. The most frequent fungi isolated were *Candida* spp. (36; 32.4%) and *Cryptococcus* spp. (22; 19.8%), and there was an association between infection with these fungi and mortality (p<0.05; OR: 7.61 and 5.53, respectively). Regarding antifungal therapy indication, 56 (50.4%) patients received it as empirical therapy, 33 (29.7%) as targeted therapy, and 22 (19.8%) as preemptive therapy. **Conclusion:** The factors that contributed to mortality of the patients were longer hospital stays, AIDS, antibacterial medication use, mechanical ventilation, and presence of a nasoenteral tube. The type of antifungal therapy used did not influence the mortality in these patients.

Keywords: *Antifungal therapies, Invasive fungal infection, Mortality, Drug therapy.*

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RESUMO

Justificativa e Objetivos: As infecções fúngicas invasivas apresentam alta morbimortalidade para pacientes hospitalizados, inclusive para aqueles em uso de terapia apropriada. O objetivo foi avaliar a terapia antifúngica profilática e preemptiva, as características clínicas e epidemiológicas, e a mortalidade de pacientes internados em uma enfermaria de doenças infecciosas de um hospital público de alta complexidade de Uberlândia, Minas Gerais, Brasil. **Métodos:** Trata-se de estudo retrospectivo realizado em uma enfermaria de doenças infecciosas. Os dados coletados dos prontuários foram referentes aos pacientes internados nos anos de 2019 e 2020 e que fizeram uso de antifúngicos azólicos (fluconazol, itraconazol ou voriconazol), equinocandinas (anidulafungina) e poliênicos (anfotericina B). **Resultados:** Durante o período, 111 pacientes usaram um ou mais antifúngicos. O tempo de internação (29,35 dias, p= 0,0252), média de dias de uso de antibacterianos (23,5 dias; p=0,0164), aids (p=0,0397), uso de ventilação mecânica (VM; p <0,001) e uso de sonda nasoenteral (p<0,01) foram variáveis que se relacionaram com desfecho morte. A infecção por fungos foi confirmada em cultura para 79 (71,2%) pacientes em terapia antifúngica. Os fungos mais frequentes foram *Candida* spp. (36; 32,4%) e *Cryptococcus* spp. (22; 19,8%), mostrando relação da infecção por esses fungos com a mortalidade (p<0,05; OR: 7,61 e 5,53, respectivamente). Quanto à terapia, 56 (50,4%) pacientes estavam em terapia empírica; 33 (29,7%) usaram como terapia alvo; e 22 (19,8%) usavam como terapia preemptiva. **Conclusão:** A mortalidade foi mais frequente entre os pacientes com maior tempo de hospitalização, que tinham aids e que fizeram uso de antibióticos, de ventilação mecânica e de sonda nasoenteral em algum momento da internação. O tipo de terapia antifúngica não influenciou a mortalidade desses pacientes.

Descritores: *Antifúngicos; Infecções Fúngicas Invasivas; Mortalidade; Tratamento Farmacológico.*

RESUMEN

Justificación y Objetivos: Las infecciones fúngicas invasivas presentan una alta morbilidad y mortalidad en los pacientes hospitalizados, incluidos aquellos que utilizan la terapia adecuada. El objetivo fue evaluar la terapia antimicótica profiláctica y preventiva, las características clínicas, epidemiológicas y la mortalidad de pacientes ingresados en una sala de enfermedades infecciosas de un hospital público de alta complejidad en Uberlândia, Minas Gerais, Brasil. **Métodos:** Este es un estudio retrospectivo realizado en la sala de enfermedades infecciosas de un hospital universitario público en Brasil. Los datos recogidos de las historias clínicas se referían a pacientes hospitalizados en 2019 y 2020 y que utilizaban antifúngicos azoles (fluconazol, itraconazol o voriconazol), equinocandinas (anidulafungina) y polienos (anfotericina B). **Resultados:** Durante el período, 111 pacientes usaron uno o más antifúngicos. El tiempo de estancia hospitalaria (29,35 días, p= 0,0252), promedio de días de uso de antibacteriano (23,5 días; p=0,0164), SIDA (p=0,0397), uso de ventilación mecánica (VM; p<0,001) y uso de sonda nasoenteral (p<0,01) fueron variables que se relacionaron con el desenlace de muerte. La infección por hongos se confirmó en cultivo en 79 (71,2%) pacientes que usaban medicamentos antimicóticos. Los agentes fúngicos más frecuentes fueron *Candida* spp. (36; 32,4%) y *Cryptococcus* spp. (22; 19,8%), mostrando relación entre la infección por estos hongos y la mortalidad (p<0,05; 7,61 y 5,53, respectivamente). En cuanto a la terapia, 56 (50,4%) pacientes estaban en terapia empírica; 33 (29,7%) la utilizaron como terapia diana; y 22 (19,8%) la utilizaron como terapia preventiva. **Conclusión:** La mortalidad fue más frecuente entre los pacientes con mayor tiempo de internación, que tenían SIDA y que utilizaron antibióticos, ventilación mecánica y sonda nasoenteral en algún momento de la internación. El tipo de terapia antifúngica no influyó en la mortalidad de estos pacientes.

Palabras Clave*: Antifúngicos; Infecciónes Fúngicas Invasoras; Mortalidad; Quimioterapia.*

INTRODUCTION

Invasive fungal infections (IFI) are a growing problem in hospitals, and it is estimated that more than 300 million people worldwide acquire fungal infections each year. Fungal infections are associated with an estimated one to two million deaths per year, a figure approaching the number of deaths due to malaria or tuberculosis.[1,2]

The prevalence of fungal infections is influenced by several factors related to the agent and the host. One of the most key factors contributing to the increase in number and severity of IFI is permanent or transient immunosuppression.[1,3] The infectious load and virulence of the fungus are principal factors which allow the fungus to establish itself in the tissue and cause infection.[3]

Although the epidemiology of fungal diseases has changed in recent decades, *Candida* spp., *Cryptococcus* spp., *Aspergillus* spp. and *Histoplasma capsulatum* continue to account for the majority of IFI. [1,4] These infections have high mortality rates: 38–75% in infection with *Candida* spp.;[5,6] 20–70% with *Cryptococcus* spp.; [7–9] 30–95% with *Aspergillus* spp.; and 26.2–47.4% in infection with *Histoplasma* capsulatum.[7,10,11]

Despite recent advances in the diagnosis and treatment of IFI, the morbidity and mortality from these infections remains very high, mainly due to delays in diagnosis and initiation of antifungal treatment. These two factors are the most important predictors of survival in patients with these infections.[4,12] Antifungal therapy is initiated according to clinical suspicion, the clinical setting, and the infectious agent.[13]

In Brazil, the classes of antifungals that are approved by the National Health Surveillance Agency (ANVISA) include imidazoles (ketoconazole), triazoles (fluconazole, itraconazole, isavuconazole, posaconazole, and voriconazole), polyenes (amphotericin B deoxycholate, amphotericin B complex lipid, and liposomal amphotericin B), and echinocandins (micafungin, caspofungin, and anidulafungin).[14–16]

Antifungal therapy can be prophylactic, empirical, preemptive, or targeted.[13] Prophylactic therapy aims to reduce the frequency of infection, particularly severe ones, when there is no currently suspected or diagnosed fungal infection, only an increased possibility of its occurrence.[13] Empirical therapy is proposed to treat a possible fungal infection before it progresses to overt disease.[13] The preemptive strategy is used when there is at least one marker of infection, such as a positive test for 1-3-β-D-glucan or for galactomannan; detection of the fungus by molecular techniques such as by polymerase chain reaction (PCR); or radiological data such as chest and sinus scans and clinical data suggesting infection. [13,17,18] Targeted therapy is used when the presence of the infective agent has been demonstrated and it has been identified by culture.[13]

Studies have been conducted to produce evidence about prophylactic and pre-emptive antifungal therapy, mainly in populations that are at high-risk of fungal infections.[19] A study by Çaglar et al.[20] evaluated antifungal therapy use in a pediatric population in Turkey. In their sample, 48.8% of patients used prophylactic therapy and another 51.2% had used the treatment (50% empirical therapy; 18.8% preemptive; 31.2% targeted therapy). Antifungal treatment strategies aim to implement the most appropriate therapy for the patient, at the right time, to reduce the risk of death. However, they also promote the safe and rational use of drugs and avoidance of excessive use, especially among immunocompromised and high-risk populations, such as transplanted and neutropenic patients.[20]

Given the high morbidity and mortality of IFI and the increase in the occurrence of patients at risk of developing these infections, the use of antifungal medications has increased. These treatments are largely empirical, such that the frequency of inappropriate prescription may also have increased.[1,12,13,19,20] Appropriate antifungal therapy impacts on the clinical outcomes of the patient, leading to shorter hospital stays, fewer complications, reduced risk of hospital outbreaks, and reduced hospital costs. This study aimed to explore the association between the outcomes of patients hospitalized in an infectious diseases' unit and the type of antifungal therapy they were treated with, by evaluating prophylactic and preemptive antifungal therapies, clinical and epidemiological features, and the mortality of patients admitted to an infectious diseases ward of a public high complexity hospital in Uberlandia, Minas Gerais, Brazil.

METHODS

This is a retrospective and observational study conducted in the specialized infectious diseases ward of the Clinical Hospital of the Uberlandia, Federal University of Uberlandia, a public high complexity university hospital in the state of Minas Gerais, Brazil. The hospital has 520 beds, 16 of which belong to the infectious diseases ward.

Patient demographic and clinical data, laboratory and imaging test results, medical reports, and other information contained in the medical records were collected from the Hospital Information System (HIS). The data collected were: age; sex; length of hospitalization; diagnosis; chief complaint; whether they were a transplant patient; comorbidities such as HIV/AIDS, diabetes, systemic arterial hypertension, neoplasms, or other comorbidities; vital data; use of invasive mechanical ventilation; parenteral nutrition; use of a catheter or probe during hospitalization; results of blood culture, urine, cerebrospinal fluid (CSF), bone marrow aspirate, bronchial aspirate, sputum, imaging and biopsy results; microorganisms isolated; antifungals and antibacterial drugs prescribed and the time of use; corticosteroid use; and outcome.

Fungal infections were identified from the culture results of clinical samples, as found in patient records. The analyses (culture and identification of fungi) were carried out in the hospital's mycology laboratory. Sample collections were conducted according to the hospital's internal protocol and identifications were carried out using classical methodology and the Vitek® system (bioMérieux-Durham, USA).

Patients aged 18 years or older who were hospitalized between January 2019 to December 2020, and taking antifungal medications (amphotericin B [deoxycholate, lipid complex, and/or liposomal], anidulafungin, fluconazole, itraconazole, micafungin, or voriconazole), were included in this study. Patients whose records were incomplete, who were discharged or died within 48 hours of admission, and those who took antifungal medications to treat leishmaniasis were excluded.

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS, software version 20). Categorical variables were reported as simple and relative frequencies. For continuous variables, measures of central tendency and dispersion (mean and standard deviation) were used. The significance level adopted was 5% ($p \leq 0.05$). The association between death/discharge (outcome) and independent variables was verified using simple and multiple logistic regressions, with a significance factor of 5%, to obtain the *Odds Ratio* (OR) and 95% confidence interval (95% CI).

This research was conducted in accordance with the required ethical standards - Resolutions 466/2012 -

510/2016 - 580/2018, of the Ministry of Health, Brazil; it was approved by the Research Ethics Committee of the Federal University of Uberlandia, Brazil (CAAE number 38317520.3.0000.5152 and approval protocol number 4.321.218 on October 5, 2020).

RESULTS

From January 2019 to December 2020, 567 patients were admitted to the specialized infectious disease ward. Of these, 111 (19.58%) received antifungal therapy. The majority were male (69.4%), with a median age of 40 years (from 18 to 88 years). Male patients had a higher frequency of survival than females (Table 1).

The length of hospital stay (p=0.0252), mean number of days of anti-bacterial use (p=0.0164), prevalence of AIDS (p=0.0397), use of mechanical ventilation (MV) (p<0.001) and use of a nasogastric tube (NGT) (p<0.01) were variables that were related to death (Table 1). AIDS was the comorbidity most strongly associated with death (p=0.0397; OR= 8.78) and was the independent variable for death occurrence (p=0.0165; OR=77.0) (Table 1).

Among the patients who underwent to invasive procedures, MV and NGT were associated with the occurrence of death (p<0.0001; OR=20.8 and p=0.0020; OR=9.10, respectively), but only MV was associated with death on multivariate analysis (p=0.0241; OR=8.8) (Table 1). Of the 111 patients who took antifungal medications, 79 (71.1%) had a fungal infection confirmed on laboratory tests or imaging. The remaining patients (n=32) received empirical therapy. The antifungal drugs fluconazole and amphotericin B were the most prescribed for both patients who had (81 and 65, respectively) and who not had a confirmed fungal infection (26 and 22, respectively). The use of anidulafungin was directly related to the occurrence of death, being statistically significant on univariate analysis for both fungal infection (p<0.01 and OR 8.36) and absence of fungal infection (p<0.01 and OR=23.7). Patients who used three different antifungal classes simultaneously had a higher occurrence of death compared to those who used only one (p=0.3027 and OR=3.72). The mean length of antifungal use was 16 days, and 76 patients (68.4%) used only one class of antifungal (Table 2).

When the occurrence of deaths was evaluated by fungal microbial agent, they were found to have occurred more frequently in patients who were infected with *Candida* spp. or *Cryptococcus* spp. Patients infected with *Candida* spp. were seven times more likely die (OR=7.61; p<0.0179) and those infected by *Cryptococcus* spp. were five times more likely to die (OR=5.53; p<0.0375) compared to other fungal agents (Table 3). Most of the fungi were isolated from blood (51 patients; 64.5%), followed by gastric aspirate (34 patients; 43%) and lung biopsy (20 patients; 25.3%). *Candida* spp. were isolated from 36 patients (32.4%), *Cryptococcus* spp. from 22 patients (19.8%), and *Histoplasma capsulatum* from 20 patients (18%). *Candida* spp. were responsible for 32.4% of infections, with *Candida albicans* being the most frequent species (21.6%). Less frequent non-*C. albicans* species were *Candida parapsilosis* (4.5%), *Candida krusei* (1.8%), *Candida glabrata* (1.8%), *Candida tropicalis* (0.9%), *Candida dubliniensis* (0.9%), and *Candida kefir* (0.9%). Figure 1 shows the frequency of fungi isolated by clinical sample type.

Empirical antifungal therapy was instituted for 56 (50.4%) patients, followed by targeted therapy (33; 29.7%) and preemptive therapy (22; 19.8%). The frequency of death was similar among patients receiving the different types of therapy: 14.3%, 13.6%, and 12.1% of those receiving empiric, preemptive, and targeted therapy, respectively, had an outcome of death (Table 3).

Table 1. Demographic and clinical characteristics of patients admitted to the infectious diseases ward who received antifungal therapy, and relationships with mortality.

	Survivors N=96		Deaths N = 15		Univariate Analysis		Multivariate analysis	
Features	**N**	**%**	**N**	**%**	**p-value**	**OR**	**p-value**	**OR**
Male	70	72.9	7	46.7	0.0471	0.33	0.0157	0.04
Female	26	27.08	8	53.3			-	-
Age (average)	43.01±15.41		39.07±14.42		0.3526	0.98	-	-
Hospitalization time (average/days)	27.46±17.06		41.47±35.04		0.0252*	1.03	-	-
Time of antibiotic use (mean/days)	20.95±19.4		39.8±40.87		0.0164*	1.03	-	-
Comorbidities								
AIDS	59	61.5	14	93.3	0.0397*	8.78	0.0165*	77.00
Diabetes mellitus	8	8.3	1	6.7	0.8263	0.79	-	-
Kidney transplantation	2	2.1	0	0	0.0993	0.00	-	-
Neoplasia	10	10.4	2	13.3	0.7358	1.32	-	-
Hypertension	22	22.9	2	13.3	0.4087	0.52	-	-
Invasive procedures								
Mechanical ventilation	5	5.2	8	53.3	0.0001*	20.80	0.0241*	28.80
Nasoenteral tube	5	5.2	5	33.3	0.0020*	9.10	-	-
Hemodialysis	0	0	3	20.0	0.9893	1.00	-	-
Parenteral Nutrition	1	1	1	6.7	0.1845	6.79	-	-

**Statistical p≤0.05; AIDS: Acquired immunodeficiency syndrome.*

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Table 2. Antifungal use in relation to the presence of laboratory-proven infection and mortality.

	Proven fungal infection present				Proven fungal infection absent			
Antifungals	**Survivors N=96 N (%)**	**Deaths N = 15 N (%)**	**Univariate Analysis p-value**	**OR**	**Survivors N=96 N (%)**	**Deaths N = 15 N (%)**	**Univariate Analysis p-value**	**OR**
Fluconazole	67 (69.7%)	14(93.3%)	0.0888	6.06	23 (23.9%)	3 (20%)	0.7368	0.79
Time of use (days)	12.06 ± 10.43	13.36± 10.75	0.6715	1.01	4.7 ± 1.69	6 ± 1.73	0.2343	1.68
Amphotericin B	57 (59.3%)	8 (53.3%)	0.4410	0.78	19 (19.7%)	3 (20%)	0.9850	1.01
Time of use (days)	18.12 ± 15.29	17 ± 13.04	0.8412	0.99	4.89 ± 2.4	6.33 ± 0.58	0.3176	1.34
Voriconazole	4 (4.1%)	0 (0)	0.7863	0.66	0 (0)	0 (0)	0.3650	6.22
Time of use (days)	23.5 ± 8.06	-	-	-	-	-	-	-
Anidulafungin	4 (4.1%)	4 (26.6%)	0.0062	8.36	1 (1.04%)	3 (20%)	0.0080*	23.75
Time of use (days)	6.86 ± 4.98	6 ± 6.16	0.7811	0.96	4 ± 0	3 ± 1.73	0.5265	0.53
Itraconazole	4 (4.1%)	0 (0)	0.7863	0.66	1 (1.04%)	0 (0)	0.6638	2.05
Time of use (days)	15.5 ± 10.75	-	-	-	4 ± 0	-	-	-
Number of antifungals								
One antifungal [a]	67 (69.8)	9 (60)	-	-	12 (12.5%)	0	-	-
Two antifungals [b]	27 (28.1)	5 (33.3)	0.5941	1.38	16 (16.6%)	3 (20%)	0.2842	5.30
Three antifungals [c]	2 (2.1)	1 (6.7)	0.3027	3.72	0 (0)	1 (6.6%)	0.0475*	75.00

**p≤0.05; [a]Amphotericin B; Fluconazole; Itraconazole; Voriconazole; [b] (Concomitant) Amphotericin B + Fluconazole; Fluconazole + Anidulafungin; Amphotericin B + Anidulafungin; [c] (Concomitant) Amphotericin B + Fluconazole + Anidulafungin.*

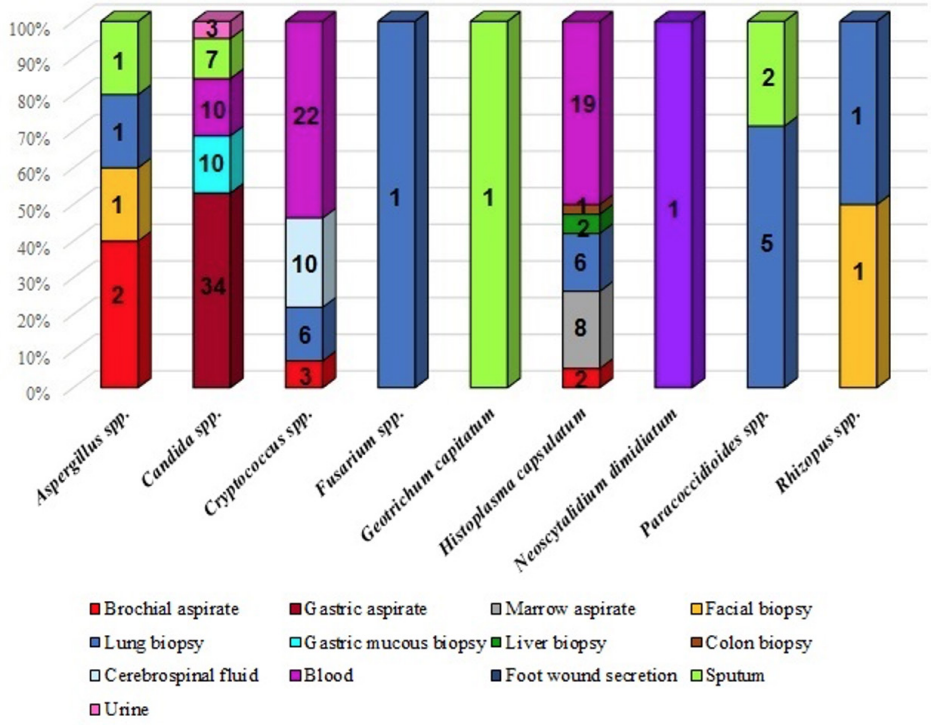

Figure 1. Frequency of fungi isolated according to clinical sample type.

DISCUSSION

This study evaluated clinical features and epidemiology, mortality, and different antifungal therapy strategies for treating patients in the infectious disease ward of a tertiary care hospital in Uberlandia, Minas Gerais, Brazil.

Most patients who were prescribed antifungal therapies had AIDS (65.7%), and this condition contributed to the deaths of most of them. Many of these patients were not on antiretroviral treatment and were diagnosed with the disease on admission. They generally had CD4 values below 200 cells/mm^3 (data not shown), which leads to a higher risk of developing opportunistic infections and is a predictor of mortality.[21,22]

In this study, the other risk factors that were related to higher mortality of patients were length of hospital stay, use of MV, use of NGT, and length of antibacterial use. Prolonged use of MV increases the risk of ventilator-associated pneumonia, as well as other complications such as sinusitis, tracheal stenosis, vocal fold

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injury, and tracheoesophageal or tracheovascular fistula.[23–25] The use of NGT also represents an increased risk of death, as has been described in the literature.[26,27] Adverse events from the use of this tube include pneumothorax, cardiorespiratory arrest, and death.[28,29] According to the Food and Drug Administration (FDA), there were 51 reports of pneumothorax between January 2012 and July 2017 related to NGT insertion.[28] The time of prolonged use of antibiotics is a relevant factor for the occurrence of co-infection by multidrug-resistant bacterial species and by fungi.[16,30,31]

IFIs are associated with high rates of morbidity, mortality, and increased length of stay and costs in the care of hospitalized patients,[16,31] so early initiation of antifungal therapy reduces complications in critically ill patients.[32,33]

Current guidelines recommend empirical antifungal therapy; however, this often offers limited benefits to patients and may result in overtreatment.[34] Some studies have demonstrated decreased mortality in patients who received empiric treatment, while others have indicated that such practice made no relevant difference in hospital mortality, suggesting that this issue is still controversial.[19,20,35] Likewise, preemptive therapy may reduce the likelihood of adverse events; the cost; and the risk of antimicrobial resistance that is associated with the use of non-selective empiric treatments. In the management of IFI, preemptive therapy has been shown to be effective. [33] However, the high costs of diagnostic tests represent a barrier to widespread use by the health system, especially in low- and middle-income countries, so the empirical strategy remains a reality in countries such as Brazil.[33]

In this study, 32 (28.8%) patients who were prescribed antifungal medications had no confirmation of IFI on laboratory or imaging tests. Data in the literature indicate a rate of 26.9 to 74% in the inappropriate use of antifungal drugs;[13,16,35] however, caution is required when comparing studies, as the clinical status of the patient, the epidemiological profile of infections, and the different institutional protocols for therapy should also be taken into consideration. In Brazil, guidelines for the control of invasive fungal infections are provided by the National Health Surveillance Agency (ANVISA), which were established in the context of the COVID-19 pandemic and published in 2021,[14] and in the Brazilian guidelines for the management of candidiasis published in 2013.[15] Institutional protocols take these documents into account, adapted according to the local context, such as patient conditions, most common fungal infections, and available antifungals.[14,15]

Patients who used three antifungal drugs simultaneously had a higher occurrence of death, and this association was greater among patients who had no proven fungal infection (OR=75.00; p<0.0475), and was likely related to the severity of the patients' conditions and empirical therapy for fungal infection. In addition to the patient's conditions (immunosuppressed, use of antifungals with recurrence, and underlying diseases), which interfere with the clinical response to antifungal therapy, tolerance or resistance to the antifungal may have contributed to the outcome.[36] Anidulafungin was the only antifungal drug whose use was correlated with death. In the hospital where the study was carried out, the indication for starting therapy with anidulafungin includes only patients who are not responsive to previously instituted antifungal treatment, or when another antifungal is contraindicated (such as amphotericin), and in those who are severely ill. In general, factors such as greater severity of the patients and late initiation of anidulafungin therapy may have contributed to higher mortality in this group.

Invasive candidemia is a condition of concern, particularly because of its high mortality rate,[35] which ranges from 52.0% to 55.9%. [37–41] The mortality in the present study was 53.3% (p<0.05 and OR=7.61). Cryptococcosis and histoplasmosis were two other diseases diagnosed among patients in the infectious disease award. Cryptococcosis is a systemic mycosis frequently diagnosed in AIDS patients and is associated with a large number of deaths.[9,42] In the present study, cryptococcosis correlated independently with the occurrence of death (p<0.05 and OR=5.53). In Brazil, mortality rates for this infection range from 26% to 70%.[42–44] Disseminated histoplasmosis is also one of the most common opportunistic diseases in HIV/AIDS patients.[45] In recent studies, the mortality caused by AIDS-associated histoplasmosis was reported to be between 33 and 56.5%.[46,47]

The incidence of patients with IFI has increased, as well as the use of antifungal drugs, mainly empirically, such that the frequency of inappropriate prescription is increasing. The appropriate and rational use of antifungal medications requires adequate protocols that are periodically reviewed to improve clinical outcomes, reduce the risk of adverse events (from drugs or drug interactions), and reduce costs to the healthcare system, adjusted to each institution's setting and considering local epidemiology. The impact of interventions should be quantified to provide feedback to programs and to be comparable with other institutions.

Some limitations of this study should be noted. Firstly, the number of patients in each group was small, especially in the monotherapy and combination therapy groups. Secondly, this was a single-center study and therefore the results may not reflect the outcome of combination therapy of antifungal agents in patients at different institutions. Thirdly, the retrospective study may bias the results. On the other hand, this study has used an approach infrequently found in the literature, which was the association between the type of fungal therapy and the outcome of the patients. Thus, new studies based on the presented protocol could be performed and improved, contributing to well-designed randomized controlled trials to address this issue in a more robust way by different institutions in different regions of the world.

In this study, mortality among patients who used antifungal therapy during hospitalization was more frequent among those with AIDS; those who had longer hospital stays; had prolonged antibiotic use; who used three different antifungal classes simultaneously; were submitted to invasive procedures (MV and NGT); and were infected by *Candida* spp. and *Cryptococcus* spp. Most

of the patients who used antifungal treatment (including empirical therapy) had a confirmed fungal infection. In conclusion, the factors that contribute with mortality of the patients were longer hospital stays, AIDS, antibacterial drug use, mechanical ventilation, and nasoenteral intubation. The type of antifungal therapy did not influence the mortality of patients.

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AUTHORS' CONTRIBUTIONS

Flávia Maria Pinto Monteiro Antonieti, **Denise Von Dolinger de Brito Roder** and **Reginaldo dos Santos Pedroso** contributed to the conception, design of the article, analysis and writing of the article.**Flávia Maria Pinto Monteiro Antonieti**, **Denise Von Dolinger de Brito Roder**, **Lúcio Borges de Araújo** and **Reginaldo dos Santos Pedroso** contributed to the planning and design of the article, review and final approval of the article.

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ORIGINAL ARTICLE

Infections in patients hospitalized for external causes in Intensive Care Units

Infecções em pacientes internados por causas externas em Unidades de Terapia Intensiva

Infecciones en pacientes hospitalizados por causas externas en Unidades de Cuidados Intensivos

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Corresponding Author:
Roberta Laíse Gomes Leite Morais
roberta.laise@uesb.edu.br

Address: Av. José Moreira Sobrinho, Jequiezinho, Jequié - BA, 45205-490.

Gabriele de Andrade Oliveira[1];
Clarice Alves dos Santos[1];
Roberta Laíse Gomes Leite Morais[1];
Vanda Palmarella Rodrigues[1];
Juliana da Silva Oliveira[1];

[1] *Universidade Estadual do Sudoeste da Bahia (UESB), Jequié, Bahia, Brazil.*

ABSTRACT

Background and Objectives: given the great demand for hospitalization due to external causes, as well as the growing number of cases of infections in health services, it can be said that these are important issues and that they represent a huge challenge to be faced by professionals and health managers around the world. Therefore, this article aims to describe the profile of individuals hospitalized for external causes in an Intensive Care Units (ICUs) who underwent a culture test and identify the main microorganisms that cause infection. **Methods:** a cross-sectional study carried out with patients suffering from external causes, admitted to an ICU of a general hospital in Bahia. The data were analyzed using descriptive statistics, presented in absolute and relative frequencies. **Results:** a total of 259 admissions to the ICU due to external causes were identified, of which 59 (22.78%) underwent cultures, of which 48 (81.35%) were men, 43 (72.88%) were brown, 32 (54.24%) did not have a partner and 35 (59.32%) suffered transport accidents. Regarding the use of devices, 54 (91.52%) patients were on invasive mechanical ventilation, 54 (91.50%) used an indwelling urinary catheter and 54 (91.52%) had a central venous catheter. The main microorganisms identified in the culture were of the genera *Staphylococcus* (17; 28.9%) and *Pseudomonas* (10; 16.9%). **Conclusion:** it is concluded that admissions to ICU resulting from external causes in patients who underwent culture were of men, who suffered transport accidents, used invasive devices, and the main infections are related to microorganisms of the genus *Staphylococcus*.

Keywords: *Epidemiology. External Causes. Infections. Intensive Care Units.*

RESUMO

Justificativa e Objetivos: Dada a grande demanda por hospitalização devido a causas externas, assim como o crescente número de casos de infecções em serviços de saúde, pode-se dizer que esses são temas importantes e representam um enorme desafio a ser enfrentado por profissionais e gestores de saúde ao redor do mundo. Portan-

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to, este artigo tem como objetivo descrever o perfil dos indivíduos hospitalizados por causas externas em Unidades de Terapia Intensiva (UTIs) que se submeteram a um teste de cultura e identificar os principais microrganismos que causam infecção. **Métodos:** Um estudo transversal foi realizado com pacientes que sofriam de causas externas, admitidos em uma UTI de um hospital geral na Bahia. Os dados foram analisados utilizando estatísticas descritivas, apresentadas em frequências absolutas e relativas. **Resultados:** Um total de 259 internações na UTI devido a causas externas foi identificado, dos quais 59 (22,78%) foram submetidos a culturas, sendo 48 (81,35%) homens, 43 (72,88%) pardos, 32 (54,24%) não tinham parceiro e 35 (59,32%) sofreram acidentes de transporte. Em relação ao uso de dispositivos, 54 (91,52%) pacientes estavam em ventilação mecânica invasiva, 54 (91,50%) usaram cateter urinário de demora e 54 (91,52%) tinham um cateter venoso central. Os principais microrganismos identificados na cultura foram dos gêneros *Staphylococcus* (17; 28,9%) e *Pseudomonas* (10; 16,9%). **Conclusão:** Conclui-se que as internações na UTI decorrentes de causas externas em pacientes que se submeteram à cultura foram de homens, que sofreram acidentes de transporte, usaram dispositivos invasivos, e as principais infecções estão relacionadas a microrganismos do gênero *Staphylococcus*.

Palavras-chave: *Epidemiologia. Causas Externas. Infecções. Unidades de Terapia Intensiva.*

RESUMEN

Antecedentes y Objetivos: Dada la gran demanda de hospitalización debido a causas externas, así como el creciente número de casos de infecciones en servicios de salud, se puede decir que estos son temas importantes y representan un enorme desafío a enfrentar por profesionales y gestores de salud en todo el mundo. Por lo tanto, este artículo tiene como objetivo describir el perfil de los individuos hospitalizados por causas externas en Unidades de Cuidados Intensivos (UCI) que se sometieron a una prueba de cultivo e identificar los principales microorganismos que causan infección. **Métodos:** Se realizó un estudio transversal con pacientes que sufrían causas externas, admitidos en una UCI de un hospital general en Bahía. Los datos se analizaron utilizando estadísticas descriptivas, presentadas en frecuencias absolutas y relativas. **Resultados:** Se identificó un total de 259 ingresos a la UCI debido a causas externas, de los cuales 59 (22,78%) se sometieron a cultivos, de los cuales 48 (81,35%) eran hombres, 43 (72,88%) eran pardos, 32 (54,24%) no tenían pareja y 35 (59,32%) sufrieron accidentes de transporte. En cuanto al uso de dispositivos, 54 (91,52%) pacientes estaban en ventilación mecánica invasiva, 54 (91,50%) usaron catéter urinario de demora y 54 (91,52%) tenían un catéter venoso central. Los principales microorganismos identificados en el cultivo fueron del género *Staphylococcus* (17; 28,9%) y *Pseudomonas* (10; 16,9%). **Conclusión:** Se concluye que los ingresos a la UCI resultantes de causas externas en pacientes que se sometieron al cultivo fueron de hombres, que sufrieron accidentes de transporte, usaron dispositivos invasivos, y las principales infecciones están relacionadas con microorganismos del género *Staphylococcus*.

Palabras clave: *Epidemiología. Causas Externas. Infecciones. Unidades de Cuidados Intensivos.*

INTRODUCTION

External causes are one of the main reasons for the large demand for hospitalizations in the public health system. In Brazil, from 2020 to May 2023, 4,264,231 hospitalizations were registered in the Brazilian Health System Information Technology Department (DATASUS - *Departamento de Informática do Sistema Único de Saúde*), resulting from transport accidents (18.1%), assaults (3.5 %), self-harm (0.8%) and other undetermined causes (59.8%).[1]

One of the consequences of hospitalizations for external causes, especially those related to the greater degree of impairment of individuals, are infections. They have a high incidence and represent a serious public health problem due to mortality, long-term bed occupancy, repercussions regarding microbial resistance, high costs for treatments and other factors that affect patient, care team as well as health service safety.[2]

According to a publication by the interinstitutional working group organized by the Ministry of Health (MoH), infections are defined as the penetration and development or multiplication of an infectious agent in the patients' body.[3] The term "Healthcare-Associated Infections" (HAIs) is used to designate any infection acquired in a health unit after 72 hours of admission or that manifests itself after discharge, which may be related to procedures carried out during the period of hospitalization or still due to extra hospital care.[4]

The Intensive Care Unit (ICU) is identified by experts as the hospital sector that houses the highest number of HAI cases, and the immunological vulnerability profile of the patients treated and the invasive procedures that are performed must be considered.[5]

Sizing even more objectively, research reveals that, for every 100 patients admitted to hospital environments in developed countries, at least seven will contract some type of HAI, while, in developing countries, this number increases to ten.[6]

Infections are also directly related to invasive procedures, especially due to prolonged use of devices, especially the central venous catheter (CVC), indwelling urinary catheter (IUC) and invasive mechanical ventilation (IMV).[7]

Due to the increase in the frequency of hospitalizations due to external causes as well as the growing number of cases related to HAIs, it can be stated that reducing these numbers is a challenge to be faced by healthcare professionals and managers around the world, since their incidence is directly linked to morbidity and mortality rates.

Considering the above, this study set out to answer the following guiding question: what is the profile of individuals admitted to the ICU for external causes who underwent a culture test and what are the main microorganisms causing infection? The objective was to describe the profile of individuals hospitalized for external causes in the ICU who underwent culture examination and identify the main microorganisms that cause infection.

METHODS

This is an epidemiological, cross-sectional and retrospective study, originating from the project "Factors associated with multimorbidity in individuals treated in an adult intensive care unit". Data were collected from medical records of individuals hospitalized for external causes in ICUs in 2019.

The study scenario consisted of three ICUs, each with ten hospital beds, until the research period, in a general hospital in the countryside of Bahia. This hospital is recognized as a regional emergency reference unit, serving 26 municipalities.

Data collection took place between May and November 2020, through consultations of electronic medical records of patients admitted to the ICU and the respective printed results of culture tests, made available by the Hospital Infection Control Commission (HICC) sector. Medical records of patients whose reason for hospitalization was not related to external causes were excluded. The initial selection of medical records took place through the ICU admission book. Data were collected using an instrument previously developed by the researchers.

The study variables included sociodemographic characteristics: sex (male and female); ethnicity (brown, black, indigenous, yellow); marital status (married and not married); and education (elementary and secondary education). It should be noted that, regarding "white" ethnicity, no record was identified in medical records and, therefore, it was not included in the description of variables. Characteristics relating to hospitalization were: day of the week (Sunday, Monday, Tuesday, Wednesday, Thursday, Friday and Saturday); type of external causes (transport accidents, assaults, undetermined cause, intentional self-harm, sequels of external causes and other external causes of accidental trauma). Characteristics referring to condition were: surgery (elective, emergency, both types and not); vasoactive drugs (yes and no); antibiotic therapy (yes and no); IMV (yes and no); acute renal failure (yes and no); blood transfusion (yes and no); IUC (yes and no); nasogastric tube and orogastric tube (yes and no); CVC (yes and no); drain (yes and no); pressure injury (yes and no); and dressings (yes and no). Characteristics relating to culture examination were: cultures in ICU (ICU 1, ICU 2 and ICU 3); type of examination (culture and antibiogram, blood culture and urine culture and antibiogram); type of material collected (tracheal aspirate, blood, lesion secretion, urine, CVC tip and ascitic and pleural fluid); result of cultures by genus (*Staphylococcus, Pseudomonas, Acinetobacter, Klebsiella, Enterobacter, Escherichia, Serratia, Enterococcus, Proteus, Citrobacter, Mycobacterium, Pantoea, Stenotropomonas* and negative).

After data collection, the instruments were organized and tabulated using Microsoft Excel 2010® and subsequently transferred to the Statistical Package for the Social Sciences (SPSS) version 21.0, being analyzed using descriptive statistics and presented in absolute frequencies and relative.

This research follows the ethical standards required in Resolutions 466/2012, 510/2016 and 580/2018 of the MoH, being submitted by the *Universidade Estadual do Sudoeste da Bahia* (UESB) Research Ethics Committee, *campus* Jequié, Certificate of Presentation for Ethical Consideration (CAAE - *Certificado de Apresentação para Apreciação Ética*) 03324918.2.0000.0055, being approved through the Consubstantiated Opinion REC-UESB, Protocol 3,092,575 of December 18, 2018.

RESULTS

A total of 259 patients admitted to the ICU for external causes were identified during 2019, and for 59 (22.78%) patients, material was collected for culture examination. Most patients were male (48; 81.35%), brown (43; 72.88%), did not have a partner (32; 54.24%) and were admitted to the ICU on Sunday (12; 54.24%). 20.34%). The lack of records in medical records regarding education information stands out (56; 94.90%) (Table 1).

Among external causes, transport accidents are the main causes of hospitalizations (35; 59.32%), followed by other external causes of accidental trauma (15; 25.42%).

In table 2, it is observed that, among individuals admitted to ICUs due to external causes and who had samples collected for culture, 39 (66.10%) underwent emergency surgery, 40 (67.80%) received administration of vasoactive drugs (VAD) and 57 (96.6%) underwent treatment with antibiotic therapy.

As for the use of devices, 54 (91.52%) patients were on IMV, 54 (91.50%) on IUC, 54 (91.52%) on CVC, and 31 (45.76%) used drains. Most patients who underwent culture also underwent blood transfusion (35; 59.32%), developed pressure injuries (PI), and 30 (50.84%) were using some type of dressing (57; 96.60%).

Table 3 reveals that ICU 1 carried out the highest number of collections (29; 49.1%). The most common type of examination performed was culture and antibiogram (30; 50.8%), with the main type of material collected being tracheal aspirate (28; 47.2%), followed by blood material (16; 27.1%) and lesion secretion (8; 13.5%). The microorganisms most present in the results were of the genus *Staphylococcus* (17; 28,9%), followed by the genus

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Table 1. Sociodemographic characteristics of occurrences and type of external causes of individuals admitted to Intensive Care Unit for external causes and who underwent culture. Jequié, BA, Brazil, 2019.

Variables	N	%
Sex		
Male	48	81.35
Female	10	16.95
NI	1	1.70
Race/color		
Brown	43	72.88
Black	1	1.70
Indigenous	1	1.70
Yellow	0	0.00
NI	14	23.72
Marital status		
No partner	32	54.24
With partner	12	20.33
NI	15	25.43
Education		
Elementary school	2	3.40
High school	1	1.70
NI	56	94.90
Week day		
Sunday	12	20.34
Monday	9	15.26
Tuesday	3	5.09
Wednesday	7	11.85
Thursday	4	6.78
Friday	8	13.55
Saturday	6	10.17
NI	10	16.96
Types of external causes		
Transport accident	35	59.32
Aggressions	6	10.17
Undetermined cause	1	1.70
AC	0	0.00
ISH	1	1.70
SEC	0	0.00
OECAT	15	25.42

Caption: *NI = no information; AC = assistance complications; ISH = intentional self-harm; SEC = sequels of external causes; OECAT = other external causes of accidental trauma.*
Source: *Authorization of Hospital Admissions – AHA and Hospital Infection Control Commission - HICC of Hospital Geral Prado Valadares.*

Table 2. Characteristics of hospitalizations of individuals admitted to Intensive Care Unit for external causes and who underwent culture. Jequié, BA, Brazil, 2019.

Variables	N	%
Surgery		
Elective	7	11.86
Emergency	39	66.10
Both	4	6.78
No	8	13.56
NI	1	1.70
Vasoactive drugs		
Yes	40	67.80
No	18	30.50
NI	1	1.70
Antibiotic therapy		
Yes	57	96.6
No	1	1.70
NI	1	1.70
Invasive mechanical ventilation		
Yes	54	91.52
No	4	6.78
NI	1	1.70
Acute kidney failure		
Yes	11	18.64
No	46	77.96
NI	2	3.40
Blood transfusion		
Yes	35	59.32
No	20	33.88
NI	4	6.80
Indwelling urinary catheter		
Yes	54	91.50
No	4	6.80
NI	1	1.70
Nasogastric and orogastric tube		
Yes	18	30.50
No	39	66.10
NI	2	3.40
Central venous catheter		
Yes	54	91.52
No	4	6.78
NI	1	1.70
Drain		
Yes	27	45.76
No	31	52.54
NI	1	1.70
Pressure injury		
Yes	30	50.84
No	28	47.45
NI	1	1.70
Dressing		
Yes	57	96.60
No	1	1.70
NI	1	1.70

Caption: *NI = no information.*
Source: *Authorization of Hospital Admissions – AHA and Hospital Infection Control Commission - HICC of Hospital Geral Prado Valadares.*

Table 3. Univariate analysis of cultures by Intensive Care Unit, type of examination, type of material collected and results of cultures performed on patients admitted due to external causes in Intensive Care Units. Jequié, BA, Brazil, 2019.

Variables	N	%
ICU culture		
ICU 1	29	49.1
ICU 2	13	22.0
ICU 3	17	29.9
Type of examination		
Antibiogram	30	50.8
Blood culture	11	18.6
Urine culture and antibiogram	4	6.7
NI	14	23.9
Type of material collected		
Tracheal aspirate	28	47.2
Blood	16	27.1
Lesion secretion	8	13.5
Urine	4	6.7
Central venous catheter tip	1	1.7
Ascitic and pleural fluids	2	3.4
Results of cultures (by genus)		
Staphylococcus sp.	17	28.9
Pseudomonas sp.	10	16.9
Acinetobacter sp.	6	10.3
Klebsiella sp.	5	8.5
Enterobacter sp.	4	6.7
Escherichia sp.	3	5.0
Serratia sp.	3	5.0
Enterococcus sp.	2	3.4
Proteus sp.	2	3.4
Citrobacter sp.	1	1.7
Mycobacterium sp.	1	1.7
Pantoea sp.	1	1.7
Stenotrophomonas sp.	2	3.4
Negative	2	3.4

Caption: *NI = no information; ICU = Intensive Care Unit.*
Source: *Authorization of Hospital Admissions – AHA and Hospital Infection Control Commission - HICC of Hospital Geral Prado Valadares.*

DISCUSSION

Male, brown and unmarried individuals had a higher prevalence of hospitalization and cultures. These data corroborate studies that indicate a greater number of hospitalizations for external causes in male individuals.[8,9] There are few studies that demonstrate the characterization of individuals who underwent culture in ICUs; however, they pointed to the direct presence of infections, such as trauma complications and other pre-existing comorbidities.[10]

Data regarding the level of education among individuals hospitalized for external causes were highly incomplete, which compromises monitoring and critical analysis for the development of strategies related to prevention in this population.[11]

According to the day of admission to the ICU, there were a greater number of admissions on Sundays, resulting from transport accidents and other unidentified causes. These results may be related to the higher prevalence of accidents among males due to greater exposure to risky behaviors, represented by lifestyle, especially on weekends, increasing alcohol consumption, increasing the likelihood of external causes related to transport accidents.[12]

Considering that the highest prevalence of external causes arises from transport accidents, there is a need for correction of fractures, which are very common among injuries caused by some type of traumatic external cause.[13]

The time interval between the need for surgical intervention and its completion represents a great risk of infections.[14] A study carried out in Belo Horizonte points out the main risk factors associated with surgical site infections as preoperative length of hospitalization for more than 24 hours, longer duration of surgery, American Society of Anesthesiologists (ASA) index classification, with clinical status ASA II, III or IV/V and with greater Potential for Contamination of the Operative Wound (PCOW).[15]

A greater number of individuals who underwent culture for a possible diagnosis of HAI were identified among those who were using VAD and IMV. VAD are used in patients with a high degree of hemodynamic compromise. Studies describe the association between the use of VAD and IMV among patients positive for some type of infection, and also highlight the occurrence of deaths in these patients.[7]

The use of antibiotic therapy was identified in most patients suffering from external causes who underwent culture. This study does not allow us to say when drug treatment was started, whether before or after collecting material for culture, which is a worrying fact, since resistance to pathogenic microorganisms can worsen patients' condition.

A review study, which consisted of a sample of 16 articles, describes the ICU as the main sector for the occurrence of bacterial mutations associated with the indiscriminate use of antimicrobial agents, prescription failures as well as contamination of equipment by healthcare workers' hands.[16]

However, there is a need to implement a surveillance culture aimed at identifying multi-resistant microorganisms that enter healthcare institutions, generally in two ways: colonization and/or infection of patients by multi-resistant microorganisms, resulting from the selective pressure generated by antimicrobial agents.[17]

Invasive devices are considered risk factors for a greater occurrence of HAIs, especially in ICUs, such as the orotracheal tube (OTT), due to IMV, CVC, tracheostomy and IUC.[18]

Correct handling of invasive devices is necessary. Ordinance 2,616, of May 12, 1998, in its body, addresses the relevance of hand hygiene before and after carrying out invasive procedures, such as dressings, catheters, drains, probes, as violating this care when handling them may violate patient safety, leading to the risk of developing nosocomial infections.[4]

Due to the impact of HAIs, the Brazilian National Health Regulatory Agency regularly launches the Brazilian National Program for the Prevention and Control of Healthcare-Associated Infections, and one of its objec-

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tives is to support surveillance and monitoring actions of microbial resistance in health services through the identification and molecular typing of multi-resistant microorganisms. This program highlights the mandatory reporting regarding primary bloodstream infections related to the use of CVC, ventilator-associated pneumonia (VAP) and urinary tract infection (UTI) associated with the use of IUC in ICUs.[6]

In this regard, it is necessary to implement an active surveillance culture service, as this can be used to direct the standardization of antimicrobial agents in ICUs, since there is a greater risk of already colonized patients developing any of the HAIs with the microorganism already existing on their skin.[16,17]

In order to diagnose HAI, methods are used to observe clinical practices of observing the signs and symptoms presented by patients, such as hypothermia, mental confusion and homeostatic imbalance, and carrying out laboratory tests.[19]

Concerning sample collection for laboratory tests, tracheal aspirate had a higher prevalence, in line with positive results for species of microorganisms of the genera *Staphylococcus* and *Pseudomonas*, supporting a study that presents similar results.[20] ICU-acquired pneumonia is related to VAP, leading to increased length of stay and increased hospital costs.[21] A study carried out in the ICU of a hospital in Santa Catarina identified that VAP is the most common among infections associated with invasive devices, with a prevalence of 31.8% and a mortality of 51.7%, and was associated with males, IMV duration and ICU stay.[22]

In relation to microorganisms, it is noteworthy that *Pseudomonas* sp. and *Acinetobacter* sp. are pathogens frequently involved in infections when patients received excessive antimicrobial therapy. A study shows that *Klebsiella* sp. was penicillin-resistant; *Pseudomonas* sp. were imipenem-, cefepime- and ciprofloxacin-resistant; and all *Acinetobacter* were ceftazidime-resistant, followed by ceftriaxone and cefepime.[23]

The genus *Staphylococcus* contains species with a high risk of pathogenicity, such as methicillin-resistant coagulase-negative *Staphylococci* (MRSCoN), which can be found in the skin microbiota. A study carried out in a large hospital in Minas Gerais identified methicillin-resistant S. *aureus*, and carbapenem-resistant *Klebsiella pneumoniae* and *Acinetobacter baumannii* in surveillance cultures.[16]

Pseudomonas are also in the group of bacteria with a high power to cause infections. The characteristics of this gram-negative wall bacterium are a crucial factor for multidrug resistance; therefore, caution should be exercised when using antibiotic therapy.[24]

Despite being considered one of the most prevalent infections, in the present study, sample collection from the urinary site obtained a low quantity, followed by CVC tip collection. UTIs caused by fungi of the genus *Candida* have a high prevalence in ICUs, being related to the use of IUC.[25]

In addition to the constant encouragement from HICC and the Patient Safety Center for reporting HAIs, it is extremely important that the healthcare team dedicates itself to following the protocols established for infection control and prevention in healthcare. The prevention of these infections, which can lead to high morbidity and mortality rates, can be achieved through simple but effective measures, such as hand hygiene, use of Personal Protective Equipment, efficiency in sterilizing material, in addition to care with invasive procedures.[19]

It is also noteworthy that HAIs are considered a serious public health problem, as they are the most frequent adverse events associated with healthcare, having high morbidity and mortality, which consequently impacts patient safety and the quality of health services.

It is necessary to encourage the strengthening of HICC as well as the implementation of a culture of surveillance, in order to enable protocols to be implemented through the training of professionals who work in ICUs and other inpatient units, with the aim of reducing damage caused by HAIs. We emphasize, however, that this study has as limitations the under-reporting related to some sociodemographic variables and the non-identification of the susceptibility of microorganisms isolated in cultures.

Finally, we understand that external causes generate impacts on health services, and patients' clinical condition, negligent handling of invasive equipment and failure to adopt good practices in prescribing antibiotics have great repercussions for the proliferation of microorganisms in critically ill patients.

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AUTHORS' CONTRIBUTIONS

Gabriele de Andrade Oliveira contributed to the research, writing the abstract, data collection, introduction, methodology, discussion, interpretation and description of results, preparation of tables, conclusions, review and final approval of the version to be published. **Clarice Alves dos Santos** contributed to the review of abstract writing, discussion, interpretation and description of results, conclusions and final approval of the version to be published. **Roberta Laíse Gomes Leite Morais** contributed to the review of abstract writing, discussion, interpretation and description of results, conclusions and final approval of the version to be published. **Vanda Palmarella Rodrigues** contributed to the review of abstract writing, discussion, interpretation and description of results, conclusions and final approval of the version to be published**. Juliana da Silva Oliveira** contributed to the project administration and supervision, data collection and processing, interpretation and description of results, preparation of tables, conclusions, review and final approval of the version to be published.

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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ORIGINAL ARTICLE

Prevalence of bacterial infections and antimicrobial resistance profile in hospitalized patients with COVID-19

Prevalência de infecções bacterianas e perfil de resistência aos antimicrobianos em pacientes internados com COVID-19

Prevalencia de infecciones bacterianas y perfil de resistencia antimicrobiana en pacientes hospitalizados con COVID-19

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Corresponding Author:
Thaís Dias Lemos Kaiser
tdlkaiser@gmail.com

Address: Av Marechal Campos, 1468 – Maruipe, Vitória, Espírito Santo.

Jhully Pimentel[1];
Thayglerson Augusto Almeida Paixão[1];
Ana Helena Croce[1];
Évelyn Faria Zanni[1];
Thaís Dias Lemos Kaiser[2];

[1] *Faculdade Multivix, Vitória, Espírito Santo, Brazil.*
[2] *Universidade Federal do Espírito Santo, Vitória, Espírito Santo, Brazil.*

ABSTRACT

Background and Objectives: bacterial resistance is an important public health problem worldwide and is related to the indiscriminate use of antimicrobials, limiting the available therapeutic options. The COVID-19 pandemic aggravated this scenario, since the lack of a standardized therapy led to a considerable increase in the prescription of these drugs. Therefore, we proposed to investigate the prevalence of bacterial infections and the profile of antimicrobial resistance in patients diagnosed with COVID-19 as well as to point out possible risk factors. **Methods:** a retrospective study based on the analysis of medical records of patients hospitalized with COVID-19 over the age of 18. Information such as age, gender, length of stay, hospitalization unit, bacterial species and resistance profile and previous use of antimicrobials by patients diagnosed with COVID-19 were collected and analyzed using Excel® 2016. **Results:** of the 268 patients with COVID-19, 162 had suspected bacterial infections, and 26 patients (9.7%) were confirmed from positive cultures. Furthermore, around 80% of these patients underwent empirical treatment with antimicrobials, the majority of whom were male and admitted to the Intensive Care Unit. A total of 32 bacterial isolates were recovered, of which 59.4% were resistant to at least one class of antimicrobials, with 21.8% being multidrug resistant. **Conclusion:** despite the low percentage found of patients with COVID-19 who had bacterial infections and of these 21.8% were by multidrug-resistant bacteria, the reinforcement in infection prevention policies and the adequate management in the release of antimicrobials is necessary to reduce the hospital dissemination rates of such bacteria.

Keywords*: COVID-19; Bacterial Infections; Drug Resistance, Microbial; Cross Infection.*

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RESUMO

Justificativa e Objetivos: a resistência bacteriana é um importante problema de saúde pública mundial relacionado ao uso indiscriminado de antimicrobianos, limitando as opções terapêuticas disponíveis. A pandemia de COVID-19 agravou esse cenário, uma vez que a falta de uma terapia padronizada resultou no aumento considerável na prescrição desses fármacos. Diante disso, propôs-se investigar a prevalência de infecções bacterianas e o perfil de resistência aos antimicrobianos em pacientes diagnosticados com COVID-19, bem como apontar possíveis fatores de risco. **Métodos:** estudo retrospectivo baseado na análise de prontuários de pacientes internados com COVID-19 com idade superior a 18 anos. Informações como idade, gênero, tempo de internação, unidade de internação, espécie bacteriana e perfil de resistência e uso prévio de antimicrobianos pelos pacientes diagnosticados com COVID-19 foram coletadas e analisadas pelo *software* Excel® 2016. **Resultados:** dos 268 pacientes com COVID-19, 162 apresentaram suspeitas de infecções bacterianas, sendo 26 pacientes (9,7%) confirmados a partir de culturas positivas. Ainda, cerca de 80% desses pacientes realizaram tratamento empírico com antimicrobianos, sendo a maioria do sexo masculino e internados em Unidade de Terapia Intensiva. Foram recuperados um total de 32 isolados bacterianos, dos quais 59,4% apresentaram resistência a pelo menos uma classe de antimicrobianos, sendo 21,8% multidroga resistente. **Conclusão:** apesar do baixo percentual encontrado de pacientes com COVID-19 que apresentaram infecções bacterianas e, desses, 21,8% serem causados por bactérias multirresistentes, o reforço nas políticas de prevenção de infecções e o adequado gerenciamento na liberação de antimicrobianos se fazem necessários para a redução das taxas de disseminação hospitalar de tais bactérias.

Descritores: *COVID-19; Infecções Bacterianas; Resistência Microbiana a Antibióticos; Infecção Hospitalar.*

RESUMEN

Justificación y Objetivos: la resistencia bacteriana es un importante problema de salud pública en todo el mundo y está relacionada con el uso indiscriminado de antimicrobianos, lo que limita las opciones terapéuticas disponibles. La pandemia por COVID-19 agravó este escenario, ya que la falta de una terapia estandarizada llevó a un aumento considerable en la prescripción de estos fármacos. Por ello, nos propusimos investigar la prevalencia de infecciones bacterianas y el perfil de resistencia antimicrobiana en pacientes diagnosticados de COVID-19, así como señalar posibles factores de riesgo. **Métodos:** estudio retrospectivo basado en el análisis de historias clínicas de pacientes hospitalizados con COVID-19 mayores de 18 años. Información como edad, sexo, duración de la estadía, unidad de hospitalización, especies bacterianas y perfil de resistencia y uso previo de antimicrobianos por parte de pacientes diagnosticados con COVID-19 fueron recopiladas y analizadas mediante el *software* Excel® 2016. **Resultados:** de los 268 pacientes con COVID-19, 162 tenían sospecha de infección bacteriana, con 26 pacientes (9,7%) confirmada a partir de cultivos positivos. Además, alrededor del 80% de estos pacientes recibieron tratamiento empírico con antimicrobianos, la mayoría de los cuales eran hombres e ingresaron en la Unidad de Cuidados Intensivos. Se recuperaron un total de 32 aislados bacterianos, de los cuales el 59,4% eran resistentes a al menos una clase de antimicrobianos y el 21,8% eran resistentes a múltiples fármacos. **Conclusión:** a pesar del bajo porcentaje encontrado de pacientes con COVID-19 que presentaron infecciones bacterianas, y de éstas cerca del 21,8% fueron por bacterias multirresistentes, es necesario reforzar las políticas de prevención de infecciones y una gestión adecuada en la liberación de antimicrobianos para reducir las tasas de diseminación hospitalaria de dichas bacterias.

Descriptores*: COVID-19; Infecciones Bacterianas; Farmacorresistencia Microbiana; Infección Hospitalaria.*

INTRODUCTION

The COVID-19 pandemic, caused by SARS-CoV-2, was declared in March 2020 by the World Health Organization (WHO). During the second half of that same year, the virus infected around 43 million people, with around 2 million dying worldwide during this period. The global mortality rate showed a significant increase from March 11, 2020 to the end of May 2022, and more than 530 million of the world's population were affected, with around 6 million individuals dying. In Brazil, by October 2023, more than 37 million confirmed cases and approximately 706,531 deaths had been recorded, resulting in a fatality rate of 1.9%.[1,2]

Although there is still no standardized drug therapy or prophylaxis to be used in patients confirmed with COVID-19, there have constantly been prescriptions for drug "kits" including antiparasitics and antimicrobials, such as azithromycin, among others.[3,4] This approach, in addition to not having substantial scientific evidence regarding benefits for patients, can contribute to the selection of resistant bacteria. Furthermore, the use of antimicrobials has also been considered as a preventive treatment for secondary bacterial infections in patients with COVID-19, which needs to be assessed in each case.[5]

Critically ill patients require intensive care and, often, a prolonged period of hospitalization, which can lead to the emergence of Healthcare-Associated Infections (HAIs). In the case of patients with COVID-19, such infections represent one of the complications caused

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mainly by bacteria that have antimicrobial resistance genes.[5,6] Still, few data regarding the prevalence of bacterial infections in patients with COVID-19 are found, and to date, it has been observed that rates can vary from 1 to 10% among patients with COVID admitted to hospitals.[7]

Antimicrobial resistance is recognized as a global health issue, impacting the success of HAI treatment, as around 2,000 people die every day worldwide due to complications caused by these bacteria. Furthermore, the WHO estimates that the number of annual deaths due to bacterial resistance will increase to around 10 million by 2050.[8] Given this scenario, the present work proposed to investigate the prevalence of bacterial infections and the antimicrobial resistance profile in patients diagnosed with COVID-19 as well as point out possible risk factors that may be associated.

METHODS

This is a retrospective observational study, based on analysis of medical records of adult patients over 18 years old, who were hospitalized with COVID-19 from May 2020 to October 2021 and who presented secondary bacterial infections during the hospitalization period.

The research was carried out in a tertiary hospital located in Vitória, Espírito Santo. It is a hospital with a highly complex surgical profile specializing in neurosurgery, vascular and orthopedics. During the pandemic period, it did not act as a reference for COVID-19, but provided care for patients with COVID, having a separate Intensive Care Unit (ICU) for this purpose. Data analysis was carried out by collecting information from the medical records of hospitalized patients who were over 18 years old, with a diagnosis of SARS-CoV-2 confirmed by molecular biology (PCR – SARS-CoV-2 positive) and who During the hospitalization period, they presented a bacterial infection confirmed by positive culture samples after being diagnosed with COVID. Patients who already had a bacterial infection before the diagnosis of COVID-19, as well as those who, upon suspicion of infection, had negative cultures, were excluded.

In the analysis, information such as age, gender, length of stay, hospitalization unit, diagnosed bacterial infection, isolated bacteria, antimicrobial resistance profile and previous use of antimicrobials of patients diagnosed with COVID-19 were collected. The microbiology sector of the hospital's laboratory uses manual methodology and automation. The sector uses as a reference for criteria for interpreting cultures and releasing infection diagnostic reports as well as for carrying out antimicrobial susceptibility testing, the criteria established by BrCast 2020 (Brazilian Committee on Antimicrobial Susceptibility)[9] and the Brazilian National Health Regulatory Agency (ANVISA - *Agência Nacional de Vigilância Sanitária*) clinical microbiology manuals.[10] Tracheal aspirate cultures with counts equal to or greater than 106CFU/mL were considered positive, and in the case of blood cultures with growth of coagulase-negative *Staphylococcus* spp., those released with growth of an isolate of the same species in at least two samples.

The collected data were analyzed descriptively and organized in a Microsoft Excel® 2016 spreadsheet. The analyzes were represented by frequency, percentage and means. The research project was previously approved in February 2022 by the Research Ethics Committee of *Centro Universitário Multivix*, under Opinion 5.263.680 (CAAE *(Certificado de Apresentação para Apreciação Ética* - Certificate of Presentation for Ethical Consideration) 51597321.4.0000.5066). All stages of research were developed in accordance with required ethical principles (Resolutions 466/2012, 510/2016 and 580/2018 of the Ministry of Health).

RESULTS

During the period assessed, 846 patients presented clinical respiratory symptoms suspicious of SARS-CoV-2 infection, undergoing molecular testing for laboratory diagnosis. Of these, 268 (31.68%) tested positive for the virus, 145 (54.1%) men and 123 (45.9%) women. Considering the group of patients with a confirmed diagnosis of COVID-19, 162 (19.15%) had culture tests requested after the diagnosis of COVID-19 based on a suspected bacterial infection, according to the medical record. Only 26 (9.7%) of patients with COVID-19 were positive for requested bacterial cultures. Of the 26 patients, 11 (42.3%) were admitted to care units (neurosurgery, stroke and vascular) and 15 (57.7%) were in ICUs. It is worth noting that the study hospital was not a reference for receiving patients with COVID-19, however, during the pandemic period, there was an increase in the number of ICU beds to accommodate patients who were unable to find places at the reference institution.

Regarding gender, of the 26 patients, the majority were men (61.5%) and were admitted to ICUs. The profile of the population participating in the study is shown in table 1.

Table 1. Epidemiological profile of patients diagnosed with COVID-19.

Gender (n/%)	Age group (years)	Mean age	Mean hospitalization	ICU admission
Male (16/61.5%)	48 - 85	58.6	17.5 days	62.50%
Female (10/38.5%)	39 - 41	62	14.2 days	50%

Of the 26 selected patients, 29 biological samples were collected, from which 32 bacterial species were isolated. More than 50% of the samples collected were representative of bloodstream infections and urinary tract infections, and 17% were isolated from respiratory samples.

Regarding the isolates, in the total cultures, there was a predominance of gram-negative bacteria (65.6%), with around 43% of the total isolates belonging to the enterobacteria group. Graph 1 shows the distribution of bacterial isolates identified in different biological materials from patients.

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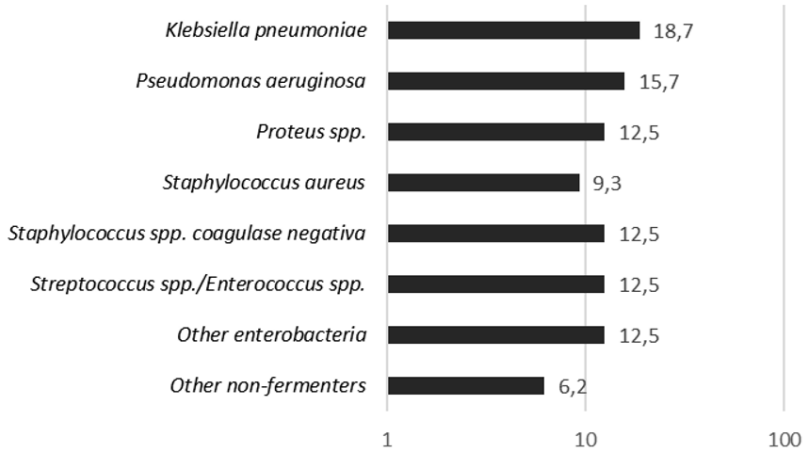

Table 1. Distribution in % of bacterial species identified from biological samples from patients with COVID-19 who presented an infectious condition.

Table 2. Percentage of antimicrobial resistance of the most common gram-negative isolates.

ATB*	*Pseudomonas* spp. n = 05	*K. pneumoniae* n = 06
AMI	2 (40%)	0 (0%)
CAZ	5 (100%)	1 (16.67%)
CIP	2 (40%)	1 (16.67%)
CPM	2 (40%)	1 (16.67%)
CRO	NT	1 (16.67%)
ERT	NT	1 (16.67%)
GEN	0 (0%)	1 (16.67%)
MER	2 (40%)	1 (16.67%)
PPT	5 (100%)	1 (16.67%)
SUT	0 (0%)	0
IMI	3 (60%)	1 (16.67%)

**Antimicrobials: AMI - amikacin; AMX - amoxicillin-clavulanate; CAZ - ceftazidime; CFL - cephalothin; CIP - ciprofloxacin; CPM - cefepime; CRO - ceftriaxone; ERT - ertapenem; GEN - gentamicin; MER - meropenem; PPT - piperacillin/tazobactam; SUT - sulfamethoxazole/trimethoprim; NT - not tested; n - number of bacterial isolates; % - percentage of resistance.*
Source: author.

When correlating species by biological material, there was a predominance of *Klebsiella pneumoniae* (37.50%) in the samples received. In blood cultures, growth was observed mainly of *Staphylococcus aureus* (27.3%), coagulase-negative *Staphylococcus* spp. (27.3%) and *Klebsiella pneumoniae* (27.3). On the other hand, in tracheal secretion samples, there was a predominance of gram-negatives, with non-fermenters (*Acinetobacter* spp., *Stenotrophmonas* spp. and *Pseudomonas aeruginosa*) making up a total of 60% of respiratory isolates.

Regarding the resistance profile, of the 32 isolates, 13 (40%) were sensitive to all antimicrobials tested and 7 (21.8%) were resistant to at least one representative in 3 or more classes of antibiotics, being classified as multidrug resistant (MDR). It was observed that, among gram-negative bacteria, 23.8% were producers of extended spectrum beta-lactamase (ESBL) and 19% were resistant to carbapenems with phenotypically confirmed carbapenemase production, namely: 1 *K. pneumoniae*, 2 *P. aeruginos*a AND 1 *A baumanii*. Among gram-positive bacteria, 57.1% of *Staphylococcus* spp. were resistant to oxacillin (methicillin-resistant *Staphylococcus* spp. - MRSA/MRS). Tables 2 and 3 show the resistance profile of the most frequent species isolated in the cultures of the patients assessed.

Table 3. Percentage of antimicrobial resistance of the most common gram-positive isolates.

ATB*	*Coagulase-negative Staphylococcus* spp. n = 04	*S. aureus* n = 03
CIP	2 (50%)	2 (66.7%)
GEN	2 (50%)	1 (33.4%)
SUT	2 (50%)	0
OXA	2 (50%)	2 (66.7%)
CLI	1 (25%)	1 (33.4%)
ERY	4 (100%)	3 (100%)
LIN	0	0
RIF	1 (25%)	0

**Antimicrobials: CIP - ciprofloxacin; GEN - gentamicin; OXA - oxacillin; LIN - linezolid; ERY - erythromycin; CLI - clindamycin; RIF - rifampicin; SUT - sulfamethoxazole/trimethoprim; n - number of bacterial isolates; % - percentage of resistance.*
Source: author.

It was observed that 22 (84.6%) of patients received preventive treatment with antimicrobials during hospitalization, but before requesting bacterial culture tests. It is worth mentioning that ten of these patients (45.4%) were infected with resistant bacteria. Regarding the drugs used in empirical treatment, 13 (50%) received piperacillin-tazobactam, ten (38.4%), vancomycin, and four (15.4%), clarithromycin.

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DISCUSSION

Critically ill patients hospitalized with COVID-19 present an important risk of developing bacterial infections of various microbiological types involving bacteria with different resistance profiles.[11,12] In the present study, a higher rate of bacterial infections was observed in men admitted to ICUs. According to the Pan American Health Organization (PAHO), one of the justifications for men being more prone to such infections than women would be that, in general, the immune response developed against the virus in women tends to be more effective and adaptive to the virus.[13] Furthermore, men tend to be less cautious about taking care to prevent virus infection.[14,15] Moreover, it is known that patients in ICUs, as they are more constantly subjected to invasive procedures, also present a greater risk of infections associated with healthcare.[16]

Our results corroborate other similar works. In a retrospective study carried out in China, a prevalence of 6.8% of bacterial infection was identified in patients with COVID-19, and of those affected, 66.7% were men.[17] In another similar study carried out in Italy, a prevalence of bacterial infections in male patients diagnosed with COVID-19 was also found to be 71.8%.[18]

Different authors found a wide spectrum of hospital infections in patients with COVID-19, the main ones being ventilator-associated pneumonia (VAP), bloodstream infections and urinary infections.[12,14] In the present study, bloodstream and urinary tract infections were the most frequent. Different factors may contribute to such secondary infections in patients infected with the SARS-CoV-2 virus. Immune compromise resulting from COVID, associated with admission to ICUs, as well as invasive procedures in these patients, such as the need for a bladder catheter, can facilitate bacterial interaction and infection development.[1,18,20]

The prevalence of infections caused by gram-negative bacteria is common, since the main bacteria associated with infection in the hospital environment belong to the *Enterobacterales* family or the group of non-fermenting gram-negative bacilli. The most prevalent bacteria in the present study (*K. pneumoniae* and *P. aeruginosa*) are frequently found in the hospital environment and have the capacity to adapt to different environments, colonizing the patients' microbiota, or contaminating surfaces, and can also be transmitted by contaminated hands.[20]

The predominance of infections by gram-negative bacteria originating from different sites was also found in other studies.[19,21,22] However, divergences were observed in these percentages of distribution by biological site, when comparing our results with other authors. A study carried out in India found a predominance of *K. pneumoniae* isolates (44% of isolates) mainly in the respiratory tract.[23] On the other hand, a study carried out in New York found a predominance of *S. aureus* in 70% of isolates from the bloodstream and respiratory secretions in patients infected with SARS-CoV-2.[24] Another work carried out in Wuhan on patients with COVID-19 who acquired secondary bacterial infections identified that, of the 159 strains isolated, 85.5% were gram-negative bacteria, with emphasis on *A. baumannii* and *K. pneumoniae*, more present in the respiratory tract and in the blood.[23]

For *P. aeruginosa isolates* from the five strains, three (60%) showed phenotypic resistance to carbapenems, while one isolate (16.7%) of *K. pneumoniae* was multiresistant, with sensitivity only to sulfamethoxazole/trimethopim and amikacin. Our results differ from those found by Li *et al*. (2020), who found 42.9% of *P. aeruginosa* species resistant to carbapenems and 76.6% of *K. pneumoniae* isolates resistant.[15] Furthermore, in a cohort study carried out on COVID-19 patients with secondary infections, resistance to carbapenems was found in 94.5% of *K. pneumoniae* isolates (n=256) isolated mainly from respiratory secretions.[25]

As for *Staphylococcus* spp. isolates (n=07), the majority were isolated from blood cultures, four (57.1%) showed resistance to oxacillin (MRSA), and, of these, two isolates were *S. aureus*. Comparable results were found in similar work in China, where around 50% of *Staphylococcus* spp. isolates were MRSA.[24] On the other hand, in the most serious scenario of the pandemic, in the city of Wuhan, it was observed that methicillin resistance was present in 100% of *S. aureus* isolates from patients with COVID-19.[17]

It was observed that 84.6% of patients assessed were previously using antimicrobials, i.e., they used these antimicrobials without the diagnosis of bacterial infection confirmed by culture. The practice of prescribing antibiotics for individuals with COVID-19 proved to be quite common during the pandemic in several countries, despite the lack of proof of their effectiveness against the virus. For instance, from March to October 2020 alone, around 80% of COVID-19 patients hospitalized worldwide received at least one antibiotic. However, the literature shows that in around 15% of cases antibiotic therapy was actually necessary, once they had a confirmed diagnosis of true bacterial infection. Several studies have already demonstrated that the selective pressures of such drugs can also contribute to the selection of bacteria resistant to existing treatments.[8,26,27]

A hospital in Napoli, Italy, when assessing 32 hospitalized patients diagnosed with SARS-CoV-2 and bacterial infections, observed that 78% of these patients had previously received antimicrobials, with piperacillin/tazobactam administered to 37.5%.[18] Meanwhile, a study identified that 97% of patients hospitalized for COVID-19 received empiric antibiotic therapy upon admission, of which 46% had bacterial infection due to carbapenem-resistant enterobacteria.[28]

In the present study, 45.4% of patients were infected with resistant bacteria. In correlation with the number of bacterial isolates, 21.8% of them were MDR. In Brazil, in 2019, the *Instituto Oswaldo Cruz* laboratory received more than 1,000 isolates of resistant bacteria from public service laboratories in several states in the country in the pre-pandemic period. In the following two years, the number of samples tripled.[21] These facts reinforce that antibiotic resistance is irreversible, as it develops in a

hospital environment, where there are several favorable factors for bacteria to acquire this profile.

Among the limitations of this study, there was a lack of information records in some patients' medical records as well as the presence of patients diagnosed with COVID-19 only through the rapid test, reducing the sample size, which also limited a better assessment of risk factors. However, being a descriptive analysis, data comparison was possible and could contribute to other studies on the topic covered.

Secondary bacterial infections in patients with COVID-19 represent a challenge for public health, and the present study highlights the reality of the high use of antimicrobials in these patients (80%). The literature is clear in establishing a relationship between the indiscriminate use of antimicrobials and antimicrobial resistance, which has seen a considerable increase during the pandemic. The prevalence of bacterial infections found, although low, is significant, as it mainly affects vulnerable patients. The fact that 21.8% of isolated bacteria are multi-resistant shows the importance of maintaining prevention policies and programs as well as the appropriate use of antimicrobials in hospitals, which are essential measures to reduce the spread and control of such infections.

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AUTHORS' CONTRIBUTIONS

Evelyn Faria Zanni, Ana Helena Croce, Thayglerson Augusto Almeida Paixão: contributed to manuscript conception, data collection, and writing. **Jhully Pimentel**: contributed to article planning and design, data collection, analysis and discussion of results and manuscript writing. **Thaís Dias Lemos Kaiser**: contributed to article planning and design, analysis and discussion of results, manuscript writing, review and correction.

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

Perceptions of the nursing team during the covid-19 pandemic: cross-sectional study

Percepções da equipe de enfermagem durante a pandemia por covid-19: estudo transversal

Percepciones del equipo de enfermería durante la pandemia de covid-19: estudio transversal

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Corresponding Author:
Ludmila Albano de Felice Gomes
ludmiladefelice@usp.br

Adress: Rua Doutor Pedreira de Freitas, Campus da USP - Ribeirão Preto (SP). CEP: 14040-900

Ludmila Albano de Felice Gomes[1];
Jéssica Fernanda Corrêa Cordeiro[1];
Daniella Corrêa Cordeiro[1];
Tatiana Areas da Cruz[1];
Denise de Andrade[1];
André Pereira dos Santos[1];

[1] *Universidade de São Paulo, Ribeirão Preto, Brasil.*

ABSTRACT

Justificativa e Objetivos: identificar as percepções dos profissionais de enfermagem que atuaram durante a pandemia de covid-19 em relação às Infecções Relacionadas à Assistência à Saúde (IRAS) e à Higienização das Mãos (HM), classificando-os por profissão e regiões brasileiras. **Método:** estudo observacional foi conduzido de novembro/2020 a dezembro/2021, com a participação de 493 profissionais de enfermagem de todas as regiões do Brasil. Utilizou-se o formulário do Google Forms®, divulgado em redes sociais. Foi aplicado um questionário intitulado "Questionário básico sobre a percepção de profissionais de saúde sobre infecções relacionadas à assistência à saúde e à higienização das mãos". Os resultados foram analisados de forma descritiva, apresentando frequências absolutas e relativas, divididos por grupos de profissionais de enfermagem (enfermeiros, técnicos e auxiliares) e por regiões do Brasil. **Resultados:** Os resultados mostraram que 43,9% dos enfermeiros relataram um impacto muito alto das IRAS na evolução clínica dos pacientes, enquanto apenas 26,7% dos auxiliares e técnicos de enfermagem compartilharam essa percepção. Em relação à HM, 50,8% dos enfermeiros consideraram que é necessário um grande esforço para realizá-la adequadamente, enquanto 68,9% dos auxiliares e técnicos de enfermagem concordaram com essa afirmação. **Conclusão:** a maioria dos profissionais de enfermagem apresentou uma alta percepção sobre HM e IRAS, levando em consideração a profissão e a região geográfica. Esses resultados podem contribuir para o desenvolvimento de estratégias futuras com o objetivo de aprimorar as práticas de HM na assistência de enfermagem, principalmente durante surtos de doenças infecciosas, como a covid-19.

Descritores: *SARS-CoV-2. Higienização das Mãos. Equipe de Enfermagem. Controle de Infecções. Educação Permanente*

ABSTRACT

Background and Objectives: to identify the perceptions of nursing professionals who worked during the covid-19 pandemic regarding Healthcare-Associated Infections (HAIs) and Hand Hygiene (HH), categorizing them by

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profession and region in Brazil. **Method:** An observational study was conducted from November 2020 to December 2021, involving 493 nursing professionals from all regions of Brazil. The Google Forms® platform, disseminated through social media was used. A questionnaire titled "Basic Questionnaire on Healthcare Professionals' Perception of Healthcare-Associated Infections and Hand Hygiene" was administered. The results were analyzed descriptively, presenting absolute and relative frequencies, divided by groups of nursing professionals (nurses, technicians, and assistants) and by regions of Brazil. **Results:** The results showed that 43.9% of nurses reported a significant impact of HAIs on the clinical progression of patients, whereas only 26.7% of nursing technicians and assistants shared this perception. Regarding HH, 50.8% of nurses considered a substantial effort necessary to perform it adequately, while 68.9% of nursing technicians and assistants agreed with this statement. **Conclusion:** most nursing professionals had a high perception of HAIs and HH, considering their profession and geographic region. These findings can contribute to the development of future strategies aimed at improving HH practices in nursing care, particularly during outbreaks of infectious diseases such as covid-19.

Keywords: *SARS-CoV-2. Hand Hygiene. Nursing Team. Infection Control. Continuing Education.*

RESUMEN

Justificación y Objetivos: identificar las percepciones de los profesionales de enfermería que trabajaron durante la pandemia de COVID-19 en relación con las Infecciones Relacionadas con la Atención de la Salud (IRAS) y la Higiene de las Manos (HM), clasificándolos por profesión y región. **Métodos:** se llevó a cabo un estudio observacional desde noviembre/2020 hasta diciembre/2021, con la participación de 493 profesionales de enfermería de las 5 regiones de Brasil. El formulario de Google® fue difundido en redes sociales. Se aplicó un cuestionario: "Cuestionario básico sobre la percepción de los profesionales de la salud sobre infecciones relacionadas con la atención de la salud y la higiene de las manos". Los resultados se analizaron de manera descriptiva, presentando frecuencias absolutas y relativas, divididos por enfermeros, técnicos y auxiliares y por regiones. **Resultados:** 43,9% de los enfermeros informaron impacto muy alto de IRAS en la evolución de los pacientes, mientras que solo 26,7% de los auxiliares y técnicos compartieron esta percepción. En cuanto a la HM, 50,8% de los enfermeros consideraron que se requiere gran esfuerzo para llevarla a cabo adecuadamente, mientras que 68,9% de los auxiliares y técnicos de enfermería estuvieron de acuerdo con esta afirmación. **Conclusión:** la mayoría de los profesionales de enfermería tuvo una percepción alta sobre las IRAS y la HM, teniendo en cuenta la profesión y la región. Esto puede contribuir al desarrollo de estrategias para mejorar las prácticas de HM en la enfermería, especialmente durante enfermedades infecciosas como el covid-19.

Palabras Clave: *SARS-CoV-2. Higiene de las manos. Equipo de Enfermería. Control de Infecciones. Educación Permanente.*

INTRODUCTION

Since the onset of the global crisis caused by Covid-19, 663,640,386 deaths have been recorded worldwide, with Brazil being the fifth country with the most deaths (36,677,844).[1] Covid-19 is caused by SARS-CoV-2, manifested by respiratory symptoms that can progress to death, transmitted by the respiratory route.[2] The survival of SARS-CoV-2 on human skin is 9 hours.[3]

Therefore, the exposure of nursing during the pandemic is undeniable, due to the use of hands as an instrument to perform care, which are vehicles for the transmission of microorganisms[4], as well as being on the front line of care.[5]

Hand hygiene (HH) refers to the action of cleaning hands in order to remove dirt and microorganisms.[6] HH inactivates SARS-CoV-23, as well as being a low-cost and effective protocol for breaking the pathogen transmission cycle.[6] After improvements at HH, there was a reduction in Healthcare-Related Infections (HAIs), which worsen the patient's condition.[7] The transmission of HAIs depends on the contamination of the hands of the professional who omits or improperly performs HH.[8] HAIs increase length of stay, mortality and hospital costs.[9] Despite initial efforts to improve HH in 2020, effectiveness was not sustained, with a drop in 2021.[10] There has been a significant increase in HAIs in the pandemic, demonstrating that the practice should be reinforced.[11]

HH is influenced by cultural and behavioral factors.[4,6] Therefore, it is crucial to evaluate the perception of nurses in relation to HH, considering the influence of these differences. The lack of knowledge is a barrier to adherence to HH, so the aim is to delineate participants' perceptions and impacts on professional behavior.[4] This study covers nursing professionals who work at different levels of care, which differs from the majority of studies, which focus on health professionals who work at more complex levels of care.

The aim of this study was to identify the perceptions of nursing professionals who worked during the covid-19 pandemic about HAIs and HH, classifying them by profession and Brazilian regions.

METHODS

This study was conducted using a cross-sectional observational design.[12] The presentation of the results

followed the Reporting of Observational Studies in Epidemiology (STROBE) and Checklist for Reporting Results of Internet E-Surveys (CHERRIES).

The sample consisted of nursing professionals (assistants, nursing technicians and nurses) in different regions of Brazil (South, Southeast, Midwest, North and Northeast). Recruitment was voluntary, through invitations published on the social networks Facebook®, Instagram®, LinkedIn® and WhatsApp®, during November/2020 to December/2021. The sample size was defined by convenience, comprising the maximum number of participants who accepted voluntarily. The inclusion criteria were: working in health care during the covid-19 pandemic, age ≥18 years and agreement to participate.

We used the "Basic questionnaire on the perception of healthcare professionals regarding healthcare-related infections and hand hygiene", developed by the World Health Organization (WHO), validated by the National Health Surveillance Agency (ANVISA) and the Pan American Health Organization (PAHO) and applied online using Google Forms®. It is self-administered, with 18 multiple-choice questions on a Likert scale.[13-15]

The results were analyzed using descriptive statistics and presented in absolute and relative frequencies, broken down by group of nursing professionals and by region. Pearson's chi-squared test (X^2) and Fisher's exact test were used to verify the association between the variables, with a significance level of $\alpha = 5\%$. Statistical analysis was carried out using the Statistical Package for the Social Sciences (SPSS) version 23 and the Reporting of Observational Studies in Epidemiology (STROBE) and Checklist for Reporting Results of Internet E-Surveys (CHERRIES) checklists were used to present the results.

The study was approved by the Research Ethics Committee of the Ribeirão Preto School of Nursing of the University of São Paulo (CEP-EERP/USP), CAAE No. 38623520.6.0000.5393, and followed the regulatory standards for research involving human beings, in accordance with Resolution CNS 466/12 of the National Health Council. Participants were informed about the objectives and methods and their right to withdraw. The study was conducted in accordance with the required ethical standards (resolutions 466/2012 - 510/2016 - 580/2018, of the Ministry of Health).

RESULTS

Sociodemographic data was collected from 493 nursing professionals. The majority were female (75.8%), from the Southeast region (74.6%) and the state of Sao Paulo (66.8%). Of the nurses, 244 (68.2%) had postgraduate degrees. The majority worked in just one place (79.3%), with 44.3% working in general care institutions in the private sector. While 27.1% of NUR had been working for less than a year, only 15.6% of nursing assistants and technicians had been working for less than a year. Only the South and North regions had more TECs than NUR. The sociodemographic description was published in a previous journal.[16] Below is the sociodemographic

Table 1. Absolute (n) and relative (%) sociodemographic characterization of the sample grouped by professional category. Brazil, 2023.

Variables	Professional Category	
	NURS	TECs
Sex		
Female	267 (74.6)	107 (79.3)
Male	91 (25.4)	28 (20.7)
Age group		
18 to 24	79 (22.1)	26 (19.3)
25 to 29	93 (26)	16 (11.9)
30 to 39	118 (33)	39 (28.9)
40 to 49	57 (15.9)	43 (31.9)
50 to 59	11 (3.1)	11 (8.1)
State of activity		
Sao Paulo	245 (68.4)	85 (63)
Acre	0	0
Maranhao	1 (0.3)	0
Minas Gerais	14 (3.9)	5 (3.7)
Bahia	14 (3.9)	3 (2.2)
Goias	5 (1.4)	0
Mato Grosso do Sul	1 (0.3)	0
Alagoas	0	0
Distrito Federal	18 (5)	4 (3)
Mato Grosso	0	0
Amapa	0	0
Espirito Santo	3 (0.8)	0
Amazonas	1 (0.3)	2 (1.5)
Ceara	3 (0.8)	1 (0.7)
Piaui	0	0
Pernambuco	10 (2.8)	1 (0.7)
Parana	4 (1.1)	1 (0.7)
Para	1 (0.3)	1 (0.7)
Paraíba	3 (0.8)	0
Rio Grande do Norte	0	1 (0.7)
Rio Grande do Sul	4 (1.1)	9 (6.7)
Rondonia	0	0
Roraima	0	0
Santa Catarina	1 (0.3)	5 (3.7)
Sergipe	1 (0.3)	0
Tocantins	0	0
Rio de Janeiro	29 (8.1)	17 (12.6)
Education		
Elementary school. 3rd cycle of basic education (9th grade)	0	2 (1.5)
High school or secondary school	2 (0.6)	92 (68.1)
Higher education. Bachelor's degree	112 (31.3)	36 (26.7)
Postgraduate. Master's or Doctorate	244 (68.2)	5 (3.7)
Number of workplaces		
1	289 (80.7)	103 (76.3)
2	55 (15.4)	26 (19.3)
3	14 (3.9)	6 (4.4)
Type of institution		
General	174 (48.6)	45 (33.3)
University	36 (10.1)	8 (5.9)
District	2 (0.6)	1 (0.7)
Emergency Room	30 (8.4)	15 (11.1)
Long Stay Institution	8 (2.2)	16 (11.9)
Primary Care Center	21 (5.9)	8 (5.9)
Home care	29 (8.1)	18 (13.3)
Obstetrics	7 (2)	4 (3)
Pediatrics	9 (2.5)	5 (3.7)
Surgical Clinic	18 (5)	7 (5.2)
Outpatient	24 (6.7)	8 (5.9)
Nature of the institution		
Public	145 (40.5)	50 (37)
Private	182 (50.8)	63 (46.7)
Public Private	31 (8.7)	22 (16.3)
Length of service (in years)		
< 1	97 (27.1)	21 (15.6)
1 to 2	52 (14.5)	23 (17)
3 to 4	42 (11.7)	18 (13.3)
5 to 6	29 (8.1)	5 (3.7)
7 to 8	23 (6.4)	11 (8.1)
9 to 10	28 (7.8)	15 (11.1)
11 to 15	31 (8.7)	14 (10.4)
16 to 20	31 (8.7)	11 (8.1)
21 to 30	25 (7)	15 (11.1)
≤ 31	97 (27.1)	2 (1.5)

Source: Author data.

Table 2. Absolute (n) and relative (%) frequency of perception of HAIs and HH by nursing professionals in the regions of Brazil and grouped by professional category. Brazil, 2023.

	General n (%)	Professional Category N (%)		Regions of Brazil N (%)				
Variables		**NUR**	**TEC**	**South**	**Southeast**	**Midwest**	**Northeast**	**North**
1. What is the average percentage of hospitalized patients in your institution who develop a healthcare-related infection?								
0% to 10%	222 (44.9)	163 (45.5)	59 (43.7)	8 (32)	182 (45.7)	11 (39.3)	17 (45.9)	4 (80)
11% to 20%	67 (13.6)	51 (14.2)	16 (11.9)	5 (20)	51 (12.8)	4 (14.3)	7 (18.9)	0
21% to 30%	60 (12.1)	49 (13.7)	11 (8.1)	2 (8)	46 (11.6)	5 (17.9)	6 (16.2)	1 (20)
31% to 40%	44 (8.9)	31 (8.7)	13 (9.6)	4 (16)	38 (9.5)	2 (7.1)	0	0
41% to 50%	19 (3.8)	13 (3.6)	6 (4.4)	1 (4)	16 (4)	0	2 (5.4)	0
51% to 60%	24 (4.9)	18 (5.0)	6 (4.4)	1 (4)	18 (4.5)	2 (7.1)	3 (8.1)	0
61% to 70%	21 (4.3)	12 (3.4)	9 (6.7)	3 (12)	15 (3.8)	2 (7.1)	1 (2.7)	0
71% to 80%	14 (2.8)	9 (2.5)	5 (3.7)	1 (4)	12 (3)	1 (3.6)	0	0
81% to 90%	11 (2.2)	8 (2.2)	3 (2.2)	0	10 (2.5)	0	1 (2.7)	0
100%	11 (2.2)	4 (1.1)	7 (5.2)	0	10 (2.5)	1 (3.6)	0	0
2. In general, what is the impact of a healthcare-related infection on the patient's clinical evolution?								
very low	32 (6.5)	21 (5.9)	11 (8.1)	1 (4)	25 (6.3)	0	5 (13.5)	1 (20)
low	58 (11.7)	33 (9.2)	25 (18.5)	3 (12)	46 (11.6)	3 (10.7)	6 (16.2)	0
high	210 (42.5)	147 (41.1)	63 (46.7)	15 (60)	163 (41)	18 (64.3)	11 (29.7)	3 (60)
very high	193 (39.1)	157 (43.9)	36 (26.7)	6 (24)	164 (41.2)	7 (25)	15 (40.5)	1 (20)
3. How effective is hand hygiene in preventing healthcare-related infections?								
very low	14 (2.8)	10 (2.8)	4 (3)	0	13 (3.3)	0	1 (2.7)	0
low	17 (3.4)	10 (2.8)	7 (5.2)	1 (4)	14 (3.5)	1 (3.6)	0	1 (20)
high	88 (17.8)	59 (16.5)	29 (21.5)	6 (24)	65 (16.3)	6 (21.4)	9 (24.3)	2 (40)
very high	374 (75.7)	279 (77.9)	95 (70.4)	18 (72)	306 (76.9)	21 (75)	27 (73)	2 (40)
4. Of all the issues related to patient safety, how important is hand hygiene in the priorities of your institution's management?								
low priority	12 (2.4)	11 (3.1)	1 (0.7)	0	11 (2.8)	0	1 (2.7)	0
moderate priority	23 (4.7)	18 (5.0)	5 (3.7)	2 (8)	16 (4)	2 (7.1)	3 (8.1)	0
high priority	123 (24.9)	92 (25.7)	31 (23)	9 (36)	95 (23.9)	8 (28.6)	11 (29.7)	5 (100)
very high priority	335 (67.8)	237 (66.2)	98 (72.6)	14 (56)	276 (69.3)	18 (64.3)	22 (59.5)	0
5. What is the percentage of cases in which healthcare professionals in your institution sanitize their hands with soap and water or alcoholic preparation when recommended?								
0% to 10%	22 (4.5)	18 (5.0)	4 (3)	0	19 (4.8)	1 (3.6)	2 (5.4)	0
11% to 20%	11 (2.2)	7 (2.0)	4 (3)	0	8 (2)	1 (3.6)	1 (2.7)	1 (20)
21% to 30%	24 (4.9)	20 (5.6)	4 (3)	5 (20)	16 (4)	1 (3.6)	2 (5.4)	0
31% to 40%	19 (3.8)	14 (3.9)	5 (3.7)	1 (4)	14 (3.5)	1 (3.6)	3 (8.1)	0
41% to 50%	43 (8.7)	32 (8.9)	11 (8.1)	2 (8)	36 (9)	1 (3.6)	4 (10.8)	0
51% to 60%	33 (6.7)	26 (7.3)	7 (5.2)	3 (12)	26 (6.5)	2 (7.1)	1 (2.7)	1 (20)
61% to 70%	42 (8.5)	33 (9.2)	9 (6.7)	0	38 (9.5)	2 (7.1)	2 (5.4)	0
71% to 80%	77 (15.6)	55 (15.4)	22 (16.3)	3 (12)	62 (15.6)	5 (17.9)	6 (16.2)	1 (20)
81% to 90%	144 (29.1)	105 (29.3)	39 (28.9)	7 (28)	119 (29.9)	9 (32.1)	8 (21.6)	1 (20)
100%	78 (15.8)	48 (13.4)	30 (22.2)	4 (16)	60 (15.1)	5 (17.9)	8 (21.6)	1 (20)
6. In your opinion, how effective would the following actions be in permanently increasing adherence to hand hygiene practices in your institution?								
a. Your institution's leaders openly support and promote hand hygiene								
1 (not effective)	9 (1.8)	4 (1.1)	5 (3.7)	1 (4)	8 (2)	0	0	0
2	11 (2.2)	11 (3.1)	9 (6.7)	0	8 (2)	2 (7.1)	1 (2.7)	0
3	40 (8.1)	31 (8.7)	24 (17.8)	2 (8)	36 (9)	1 (3.6)	1 (2.7)	0
4	92 (18.6)	68 (19)	97 (71.9)	4 (16)	70 (17.6)	7 (25)	9 (24.3)	2 (40)
5 (very effective)	341 (69.0)	244 (68.2)	5 (3.7)	18 (72)	276 (69.3)	18 (64.3)	26 (70.3)	3 (60)

b. The health service provides alcohol preparation for hand hygiene								
1 (not effective)	4 (0.8)	4 (1.1)	1 (0.7)	0	4 (1)	0	0	0
2	5 (1.0)	4 (1.1)	11 (8.1)	1 (4)	3 (0.8)	0	1 (2.7)	0
3	26 (5.3)	15 (4.2)	13 (9.6)	4 (16)	17 (4.3)	1 (3.6)	3 (8.1)	1 (20)
4	55 (11.1)	42 (11.7)	110 (81.5)	1 (4)	44 (11.1)	5 (17.9)	4 (10.8)	1 (20)
5 (very effective)	403 (81.6)	293 (81.8)	1 (0.7)	19 (76)	330 (82.9)	22 (78.6)	29 (78.4)	3 (60)
c. Hand hygiene posters are displayed at the point of care/treatment to serve as reminders								
1 (not effective)	17 (3.4)	13 (3.6)	4 (3)	1 (4)	13 (3.3)	1 (3.6)	2 (5.4)	0
2	18 (3.6)	12 (3.4)	6 (4.4)	4 (16)	13 (3.3)	0	0	1 (20)
3	48 (9.7)	38 (10.6)	10 (7.4)	1 (4)	44 (11.1)	1 (3.6)	2 (5.4)	0
4	73 (14.8)	62 (17.3)	11 (8.1)	4 (16)	53 (13.3)	8 (28.6)	7 (18.9)	1 (20)
5 (very effective)	337 (68.2)	233 (65.1)	104 (77)	15 (60)	275 (69.1)	18 (64.3)	26 (70.3)	3 (60)
d. Every healthcare professional is trained in hand hygiene.								
1 (not effective)	13 (2.6)	6 (1.7)	7 (5.2)	1 (4)	11 (2.8)	0	1 (2.7)	0
2	14 (2.8)	11 (3.1)	3 (2.2)	2 (8)	10 (2.5)	0	2 (5.4)	0
3	46 (9.3)	33 (9.2)	13 (9.6)	2 (8)	37 (9.3)	5 (17.9)	2 (5.4)	0
4	67 (13.6)	53 (14.8)	14 (10.4)	2 (8)	54 (13.6)	5 (17.9)	5 (13.5)	1 (20)
5 (very effective)	353 (71.5)	255 (71.2)	98 (72.6)	18 (72)	286 (71.9)	18 (64.3)	27 (73)	4 (80)
e. Clear and simple instructions on hand hygiene visible to each healthcare professional								
1 (not effective)	11 (2.2)	7 (2)	4 (3)	1 (4)	8 (2)	1 (3.6)	1 (2.7)	0
2	11 (2.2)	7 (2)	4 (3)	2 (8)	8 (2)	0	0	1 (20)
3	38 (7.7)	28 (7.8)	10 (7.4)	4 (16)	28 (7)	1 (3.6)	5 (13.5)	0
4	81 (16.4)	67 (18.7)	14 (10.4)	3 (12)	66 (16.6)	7 (25)	5 (13.5)	0
5 (very effective)	352 (71.3)	249 (69.6)	103 (76.3)	15 (60)	288 (72.4)	19 (67.9)	26 (70.3)	4 (80)
f. Health professionals regularly receive results of their own hand hygiene performance								
1 (not effective)	70 (14.2)	48 (13.4)	22 (16.3)	4 (16)	57 (14.3)	3 (10.7)	6 (16.2)	0
2	36 (7.3)	24 (6.7)	12 (8.9)	3 (12)	28 (7)	1 (3.6)	3 (8.1)	1 (20)
3	100 (20.2)	69 (19.3)	31 (23)	3 (12)	77 (19.3)	11 (39.3)	9 (24.3)	0
4	53 (10.7)	36 (10.1)	17 (12.6)	1 (4)	43 (10.8)	5 (17.9)	3 (8.1)	1 (20)
5 (very effective)	234 (47.4)	181 (50.6)	53 (39.3)	14 (56)	193 (48.5)	8 (28.6)	16 (43.2)	3 (60)
g. You practice perfect hand hygiene (being a good example to your colleagues)								
1 (not effective)	1 (0.2)	1 (0.3)	11 (8.1)	0	1 (0.3)	0	0	0
2	4 (0.8)	4 (1.1)	29 (21.5)	0	3 (0.8)	0	1 (2.7)	0
3	33 (6.7)	22 (6.1)	95 (70.4)	2 (8)	28 (7)	0	3 (8.1)	0
4	130 (26.3)	101 (28.2)	11 (8.1)	7 (28)	100 (25.1)	11 (39.3)	11 (29.7)	1 (20)
5 (very effective)	325 (65.8)	230 (64.2)	29 (21.5)	16 (64)	266 (66.8)	17 (60.7)	22 (59.5)	4 (80)
h. Patients are encouraged to remind healthcare professionals to sanitize their hands.								
1 (not effective)	73 (14.8)	47 (13.1)	26 (19.3)	5 (20)	58 (14.6)	3 (10.7)	6 (16.2)	1 (20)
2	54 (10.9)	39 (10.9)	15 (11.1)	3 (12)	43 (10.8)	4 (14.3)	4 (10.8)	0
3	86 (17.4)	65 (18.2)	21 (15.6)	4 (16)	71 (17.8)	6 (21.4)	5 (13.5)	0
4	56 (11.3)	38 (10.6)	18 (13.3)	2 (8)	47 (11.8)	2 (7.1)	4 (10.8)	1 (20)
5 (very effective)	224 (45.3)	169 (47.2)	55 (40.7)	11 (44)	179 (45)	13 (46.4)	18 (48.6)	3 (60)
7. How important is it to the head of your department/clinic that you practice excellent hand hygiene?								
1 (no importance)	40 (8.1)	26 (7.3)	14 (10.4)	5 (20)	28 (7)	1 (3.6)	4 (10.8)	2 (40)
2	26 (5.3)	22 (6.1)	4 (3)	1 (4)	22 (5.5)	1 (3.6)	2 (5.4)	0
3	65 (13.2)	50 (14)	15 (11.1)	3 (12)	52 (13.1)	6 (21.4)	4 (10.8)	0
4	74 (15.0)	57 (15.9)	17 (12.6)	3 (12)	60 (15.1)	4 (14.3)	7 (18.9)	0
5 (very important)	288 (58.3)	203 (56.7)	85 (63)	13 (52)	236 59.3)	16 (57.1)	20 (54.1)	3 (60)

8. How important do your colleagues think it is that you practice excellent hand hygiene?								
1 (no importance)	30 (6.1)	22 (6.1)	8 (5.9)	3 (12)	22 (5.5)	1 (3.6)	3 (8.1)	1 (20)
2	30 (6.1)	22 (6.1)	8 (5.9)	2 (8)	27 (6.8)	0	1 (2.7)	0
3	94 (19.0)	70 (19.6)	24 (17.8)	3 (12)	80 (20.1)	6 (21.4)	5 (13.5)	0
4	101 (20.4)	76 (21.2)	25 (18.5)	5 (20)	75 (18.8)	8 (28.6)	13 (35.1)	0
5 (very important)	238 (48.2)	168 (46.9)	70 (51.9)	12 (48)	194 (48.7)	13 (46.4)	15 (40.5)	4 (80)
9. How important patients think it is that you practice excellent hand hygiene?								
1 (no importance)	23 (4.7)	14 (3.9)	9 (6.7)	1 (4)	19 (4.8)	1 (3.6)	2 (5.4)	0
2	29 (5.9)	24 (6.7)	5 (3.7)	2 (8)	23 (5.8)	2 (7.1)	2 (5.4)	0
3	81 (16.4)	61 (17)	20 (14.8)	2 (8)	70 (17.6)	4 (14.3)	4 (10.8)	1 (20)
4	83 (16.8)	68 (19)	15 (11.1)	5 (20)	63 (15.8)	5 (17.9)	9 (24.3)	1 (20)
5 (very important)	277 (56.1)	191 (53.4)	86 (63.7)	15 (60)	223 (56)	16 (57.1)	20 (54.1)	3 (60)
10. How do you rate the efforts required to perform good hand hygiene when caring for patients?								
1 (no importance)	50 (10.1)	35 (9.8)	15 (11.1)	2 (8)	40 (10.1)	2 (7.1)	4 (10.8)	2 (40)
2	30 (6.1)	26 (7.3)	4 (3)	1 (4)	26 (6.5)	2 (7.1)	1 (2.7)	0
3	53 (10.7)	47 (13.1)	6 (4.4)	2 (8)	45 (11.3)	5 (17.9)	1 (2.7)	0
4	85 (17.2)	68 (19)	17 (12.6)	7 (28)	59 (14.8)	6 (21.4)	12 (32.4)	1 (20)
5 (very important)	275 (55.7)	182 (50.8)	93 (68.9)	13 (52)	228 (57.3)	13 (46.4)	19 (51.4)	2 (40)
11. What is the average percentage of cases in which you sanitize your hands either by rubbing them with alcohol or by sanitizing your hands with soap and water when recommended?								
0% to 10%	8 (1.6)	8 (2.2)	1 (0.7)	0	8 (2)	0	0	0
11% to 20%	4 (0.8)	3 (0.8)	1 (0.7)	0	4 (1)	0	0	0
21% to 30%	3 (0.6)	2 (0.6)	2 (1.5)	3 (1)	1 (0.3)	0	1 (2.7)	0
31% to 40%	12 (2.4)	10 (2.8)	1 (0.7)	4 (2)	7 (1.8)	1 (3.6)	2 (5.4)	0
41% to 50%	4 (0.8)	3 (0.8)	1 (0.7)	0	4 (1)	0	0	0
51% to 60%	17 (3.4)	16 (4.5)	7 (5.2)	0	13 (3.3)	1 (3.6)	3 (8.1)	0
61% to 70%	18 (3.6)	11 (3.1)	14 (10.4)	0	15 (3.8)	1 (3.6)	2 (5.4)	0
71% to 80%	45 (9.1)	31 (8.7)	39 (28.9)	4 (16)	39 (9.8)	0	2 (5.4)	0
81% to 90%	177 (35.8)	138 (38.5)	69 (51.1)	5 (20)	152 (38.2)	14 (50)	5 (13.5)	1 (20)
100%	205 (41.5)	136 (38)	1 (0.7)	13 (52)	155 (38.9)	11 (39.3)	22 (59.5)	4 (80)

Source: Author data

characterization with absolute and relative frequency subdivided into NUR and NUR.

Below are data by professional category and Brazilian regions. While 43.9% of nurses (NUR) said that the impact of HAIs on the patient's clinical evolution is very high, only 26.7% of nursing technicians and assistants (TEC) said the same. While 50.8% of NUR said that it takes a lot of effort to perform HH properly, only 68.9% of TECs said the same.

DISCUSSION

The sociodemographic and occupational characteristics of the participants in this study are in line with the literature. Most of the participants (374; 75.8%) were female, aged between 30 and 39 (157; 31.8%), and were nurses (358; 72.6%).[17,18]

Most nursing professionals in this study had a high perception of HH and HAI. A study carried out in Iran showed that most nursing professionals had a good perception of HH and HAI.[17] In this study, 157 (43.9%) of the nurses recognized that the impact of HAIs is very high and only 36 (26.7%) of the nursing assistants and technicians said the same. While 93 (68.9%) of the assistants and technicians said that a great deal of effort was needed to carry out a good HH, 182 (50.8%) of the nurses reported the same.

The professionals' perception is related to the level of training they have had access to.[17] Therefore, the greater effort to perform a good HH and the level of perception observed in this study can be justified, given that 249 (50.4%) have postgraduate degrees.

It was observed that 222 (44.9%) of the participants reported that only 0% to 10%

of the patients admitted to the institution where they work develop HAIs. Although there is evidence that higher levels of perception contribute to better adherence to protocols,[19] in contrast to the 374 (75.7%) who recognize the efficacy of HH in reducing HAIs, 288 (58.41%) do not perform HH in 100% of the recommended cases. Therefore, there is a contradiction between the high level of perception, the lower adherence to HH and the low development of HAIs within the institution where they work.

There is evidence that patient feedback improves professionals' HH.[20] In agreement, 277 (56.1%) participants said that patients attach great importance to HH and 224 (45.3%) considered it effective to encourage patients to remind health professionals to perform it. In addition, only 78 (15.8%) said that colleagues in the institution carry out HH in 100% of recommended cases, showing a possible lack of encouragement and example among peers, due to the influence of other professionals on their own clinical practice.[21]

Most of the participants in this and another study[18] pointed to several strategies as very effective for permanently increasing HH in institutions, such as support from leaders, reminders and HH education. This is because these strategies provide reflections and improvements on HH itself.[22] Authors emphasizes that physical structure and the availability of materials are essential for adequate HH, although studies point to a lack of resources.[23]

The perceptions of HAIs and HH described collaborated to identify possible facilitators in the practice of HH, from the perspective of nursing professionals. Considering the fundamental role of HH and nursing in reducing HAIs, the results may contribute to the development of future strategies aimed at improving HH practices in nursing care in global emergencies, such as the COVID-19 pandemic. No association was found between region and level of perception in this study, which only included nursing professionals working during the pandemic. It is worth noting that most of the participants were from the southeast and the state of São Paulo. Although the purpose of the study was to reach all Brazilian regions, some states did not respond to the questionnaire and the other regions had few responses. Although this limitation of the sample is not representative, it offers an initial view of how these aspects may be reflected in the different states and regions. In this context, it suggests the need to carry out similar studies with larger and more representative samples. The data collection period was justified by the difficulty in keeping up with new evidence and changes in the face of outbreaks of infectious diseases, such as COVID-19.[19] The remote modality overcame geographical barriers. The instrument used for data collection is easy to apply and could be reproduced in other studies. However, daily reminders were necessary to ensure the volunteers' participation, and the use of an online, self-administered questionnaire compromised the veracity of the answers.

In addition, it should be noted that most nursing professionals had a high perception of HH and HAI, considering their profession and geographical region. These results may contribute to the development of future strategies aimed at improving HH practices in nursing care, especially during outbreaks of infectious diseases such as COVID-19.

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AUTHORS' CONTRIBUTIONS

Ludmila Albano de Felice Gomes contributed to the bibliographic research, writing the summary, introduction, methodology, discussion, interpretation and description of results, preparation of tables, conclusions, review and statistics. **Jéssica Fernanda Corrêa Cordeiro** contributed to project administration, bibliographic research, writing the abstract, introduction, methodology, discussion, interpretation and description of results, conclusions, review and statistics. **Daniela Corrêa Cordeiro** contributed to writing the summary, methodology, interpretation of results, conclusions, review and statistics. **Tatiana Areas da Cruz** contributed to writing the summary, review and statistics. **Denise de Andrade** contributed to project administration, funding acquisition, literature research, review and statistics. **André Pereira dos Santos** contributed to project administration, bibliographic research, writing the abstract, introduction, methodology, discussion, interpretation and description of results, conclusions, review and statistics.

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ORIGINAL ARTICLE

Hand hygiene knowledge among nursing professionals during a pandemic: insights from a cross-sectional study in Brazil

Conhecimento sobre higiene das mãos entre profissionais de enfermagem durante uma pandemia: insights de um estudo transversal no Brasil

Conocimiento de higiene de manos entre profesionales de enfermería durante una pandemia: perspectivas de un estudio transversal en Brasil

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Corresponding Author:
Jéssica Fernanda Corrêa Cordeiro
jessica.cordeiro@alumni.usp.br

Address: Avenida dos Bandeirantes, 3900, University Campus - Monte Alegre District Ribeirão Preto - SP - Brazil

Jéssica Fernanda Corrêa Cordeiro[1];
Daniella Corrêa Cordeiro[1];
Ludmila Albano de Felice Gomes[1];
Tatiana Areas da Cruz[1];
Marilia Duarte Valim[2];
Denise de Andrade[1];
André Pereira dos Santos[1];

[1] *Universidade de São Paulo (USP), Ribeirão Preto, São Paulo, Brazil.*
[2] *Universidade Federal do Mato Grosso (UFMT), Cuiabá, Mato Grosso, Brazil.*

ABSTRACT

Background and Objectives: hand hygiene (HH) is a crucial safety practice, but lack of knowledge can hinder compliance. The objective was to measure and assess the knowledge of nursing professionals who provided care during the COVID-19 pandemic regarding HH and to verify the association between HH knowledge and professional category and regions in Brazil. **Methods:** an observational study was conducted from November 2020 to December 2021 involving 493 nursing professionals from all regions of Brazil. Data collection was carried out using Google Forms® and social media platforms. The Hand Hygiene Knowledge Test for Healthcare Professionals was used, and results were analyzed descriptively. Pearson's chi-square test (x^2) and Fisher's exact test were employed to assess associations. **Results:** among the participants, the majority (74.7%) had limited or subpar knowledge of HH. Nurses had a higher level of knowledge compared to nursing assistants and licensed practical nurses. Associations were found between professional category and correct answers regarding microorganism destruction time and the type of HH to be used. **Conclusion:** Brazilian nursing professionals had limited knowledge of HH, with nurses displaying a higher level of knowledge compared to nursing assistants and licensed practical nurse. Continuous education and guidance are necessary to improve HH practices among the nursing staff.

Keywords: *SARS-CoV-2. Hand Hygiene. Nursing staff. Infection Control. Continuous Education.*

RESUMO

Justificativas e Objetivos: a higiene das mãos (HM) é uma prática crucial para a segurança, mas a falta de conhecimento pode prejudicar a adesão. Este estudo avaliou o conhecimento dos profissionais de enfermagem que

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prestaram cuidados durante a pandemia de Covid-19 em relação à HM e explorou a associação entre o conhecimento de HM, categoria profissional e regiões no Brasil. **Métodos:** um estudo observacional foi conduzido de novembro de 2020 a dezembro de 2021 envolvendo 493 profissionais de enfermagem de todas as regiões do Brasil. A coleta de dados foi realizada usando o *Google Forms*® e plataformas de mídia social. Foi utilizado o Teste de Conhecimento de Higiene das Mãos para Profissionais de Saúde, e os resultados foram analisados descritivamente. O teste qui-quadrado de Pearson (x^2) e o teste exato de Fisher foram empregados para avaliar as associações. **Resultados:** entre os participantes, a maioria (74,7%) tinha conhecimento limitado ou insuficiente sobre HM. Os enfermeiros apresentaram um nível mais elevado de conhecimento em comparação com os auxiliares e técnicos de enfermagem. Foram encontradas associações entre a categoria profissional e respostas corretas sobre o tempo de destruição de microrganismos e o tipo de HM a ser utilizado. **Conclusão:** os profissionais de enfermagem brasileiros possuíam conhecimento limitado sobre HM, sendo que os enfermeiros apresentaram um nível mais elevado de conhecimento em comparação com os auxiliares e técnicos de enfermagem. Educação contínua e orientação são necessárias para melhorar as práticas de HM entre a equipe de enfermagem.

Descritores: *SARS-CoV-2. Higiene das Mãos. Equipe de Enfermagem. Controle de Infecções. Educação Contínua.*

RESUMEN

Justificación e Objetivos: la higiene de manos (HM) es una práctica de seguridad crucial, pero la falta de conocimiento puede dificultar el cumplimiento. Este estudio evaluó el conocimiento de los profesionales de enfermería que brindaron atención durante la pandemia de Covid-19 en relación con la HM y exploró la asociación entre el conocimiento de HM, la categoría profesional y las regiones en Brasil. **Métodos:** se realizó un estudio observacional desde noviembre de 2020 hasta diciembre de 2021 que incluyó a 493 profesionales de enfermería de todas las regiones de Brasil. La recopilación de datos se realizó utilizando *Google Forms*® y plataformas de redes sociales. Se utilizó el Test de Conocimiento de Higiene de Manos para Profesionales de la Salud, y los resultados se analizaron de manera descriptiva. Se emplearon la prueba chi-cuadrado de Pearson (x^2) y la prueba exacta de Fisher para evaluar las asociaciones. **Resultados:** entre los participantes, la mayoría (74,7%) tenía conocimiento limitado o deficiente de HM. Las enfermeras tenían un nivel de conocimiento más alto en comparación con los auxiliares y técnicos de enfermería. Se encontraron asociaciones entre la categoría profesional y las respuestas correctas sobre el tiempo de destrucción de microorganismos y el tipo de HM que debía utilizarse. **Conclusión:** los profesionales de enfermería brasileños tenían un conocimiento limitado de HM, siendo que las enfermeras mostraban un nivel de conocimiento más alto en comparación con los auxiliares y técnicos de enfermería. Se requiere educación continua y orientación para mejorar las prácticas de HM entre el equipo de enfermería.

Palabras Clave: *SARS-CoV-2. Desinfección de Manos. Equipo de Enfermería. Control de Infecciones. Educación Continua.*

INTRODUCTION

COVID-19 is a highly contagious illness caused by the SARS-CoV-2 virus, capable of causing acute respiratory infections, severe illness, and fatalities.[1,2] The virus is mainly transmitted through respiratory droplets and aerosols,[3] and can even be transmitted through fecal matter.[4] Previous studies have demonstrated that the virus can contaminate a variety of surfaces, including chairs, tables, bed rails, stethoscopes, toilets, and floors.[1,2,4] Environmental contamination can amplify the chain of transmission.[1,2,4] Touching contaminated surfaces and subsequent contact with mucous membranes can increase the risk of contamination and virus transmission.[5] Additionally, touching the face can serve as a potential vector for self-inoculation of various pathogens.[6] The human face provides a favorable environment for the survival of enveloped viruses like influenza and coronaviruses,[7] and the SARS-CoV-2 virus has been found to remain viable on human skin for approximately 9 hours.[8]

Considering the characteristics of SARS-CoV-2, as well as other viruses, nursing staff exposure during patient care is inevitable, as healthcare requires direct contact with patients using hands, which can serve as vehicles for microorganism transmission.[9] Thirty percent of deaths among nursing professionals due to COVID-19 occur in Brazil.[10] The nursing staff works on the frontlines of care in various sectors and has faced challenges such as a shortage of personal protective equipment, supplies, and work overload.[11] Given the potential severity of COVID-19 and other diseases,[1,2] patients often require intensive care that involves aerosol-generating procedures and secretion management, such as endotracheal suctioning performed by nurse.[12]

Hand hygiene (HH) is a critical safety measure designed to eliminate dirt and microorganisms.[13] Properly conducted, HH has the ability to deactivate several viruses, including SARS-CoV-2, thus decreasing the risk of contact transmission.[8] HH is effective in pre-venting the transmission of other pathogens and significantly reducing healthcare-associated infections (HAI) that worsen

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hospitalized patients' condition.[14] HAI transmission among patients depends largely on the contamination of healthcare professionals' hands, despite there being various risk factors for the spread of infections among patients.[15] HAI are preventable, but they remain one of the most common adverse effects of healthcare, leading to increased hospitalization time, mortality, and healthcare costs.[16]

Although care and safety have been compromised due to work overload, lack of resources, and knowledge,[17] there is evidence that compliance with HH during the pandemic has shown significant improvement among healthcare professionals compared to previous years.[18] This can be explained by the scientific race to manage the pandemic and its impacts, contributing to new discoveries and investments.[19] However, improvements in HH compliance among healthcare professionals during the early stages of the pandemic were not sustained, leading to a significant decline in 2021.[20] Therefore, it is important to assess the impact of the COVID-19 pandemic on nursing professionals' knowledge regarding HH practice, as this practice is always valued in infection control. In light of the above, professionals' knowledge, attitudes, and practice regarding this health-promoting behavior should be constantly reinforced.

HH is influenced by cultural aspects, which can affect human behavior.[13] It is crucial to assess nursing professionals' knowledge during the COVID-19 pandemic, given the importance of HH in mitigating the spread of SARS-CoV-2. However, it is important to take into consideration the cultural and regional differences in the study, which can impact the level of knowledge among professionals regarding HH. This study included nursing professionals from all levels of care because it is known that pre-symptomatic and asymptomatic patients can transmit SARS-CoV-2.[21]

Lack of knowledge is a barrier to HH compliance,[7] which is why this study not only assessed sufficient knowledge but also identified knowledge gaps among professionals by regions in Brazil and professional categories. Thus, the research question was whether nursing professionals' knowledge regarding HH during the COVID-19 pandemic is adequate or deficient. These initiatives will not only benefit healthcare professionals' safety by reducing the spread of infections, including SARS-CoV-2, but also enhance the capacity to respond to future public health emergencies, minimizing the risks of pathogen transmission in healthcare settings. In light of this, the aim was to measure and assess the knowledge of nursing professionals who provided care during the COVID-19 pandemic regarding HH and to ascertain the association between HH knowledge and professional categories and regions in Brazil.

METHODS

Study Design

This is an observational cross-sectional study[22] that followed the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) and the Checklist for Reporting Results of Internet E-Surveys (CHERRIES) presentation criteria.

Sample and Procedures

The sample for this study consisted of nursing professionals (nursing assistants, licensed practical nurse, and nurses) working in nursing care across five different regions of Brazil (South, Southeast, Midwest, North, and Northeast). Participant recruitment was voluntary and conducted online through social media platforms such as Facebook®, Instagram®, LinkedIn®, and WhatsApp® from November 23, 2020 to December 23, 2021. Invitations were extended to relevant nursing groups and involved collaboration with nursing organizations. The researcher identified themselves and provided details about the research, giving a brief account of the objectives, risks, and contributions to nursing practice. The invitation was posted weekly, reaching all five regions of Brazil. As an exclusion criterion, not being a nursing professional and not currently practicing nursing at the time of the research was adopted.

The sample size was determined by convenience, corresponding to the maximum number of nursing professionals who agreed to participate in the research during the 13-month recruitment period. Professionals involved in nursing care during the COVID-19 pandemic at the time of data collection, as self-declared by participants and who belonged to relevant nursing groups and collaborated with nursing organizations, were included. The snowball method was employed, in which the link was shared and forwarded among groups. Participants were informed about the research objectives and methods and were ensured the right to withdraw at any time. To avoid duplicate answers, participants provided their email addresses. There was no identification of nursing professionals, and anonymity was preserved.

Data Collection and Questionnaires

Data collection was conducted through a self-administered questionnaire provided online using the free platform Google Forms®. The questionnaire comprised two distinct sections. One section aimed to assess sociodemographic and work-related characterization, containing 12 objective multiple-choice questions. These questions encompassed information about gender, age, educational level, number of current employments, nature of the workplace (public or private), years of professional experience, and nursing category. The other section aimed to assess professionals' technical and scientific knowledge regarding HH, comprising 47 multiple-choice, true or false, and yes or no questions. The instrument utilized to assess professionals' knowledge was the Hand Hygiene Knowledge Test for Healthcare Professionals, which was developed and validated by the Brazilian Health Regulatory Agency (ANVISA - *Agência Nacional de Vigilância Sanitária*) and the Pan American Health Organization (PAHO) in 2008.

Data Analysis

The collected data were analyzed using Google Forms® and subjected to descriptive statistical analyses, presented as absolute and relative frequencies. Considering statistical significance when p-value ≤ 0.05, association tests (Pearson's chi-square test (X^2) and Fisher's exact test) were performed between the number of correct answers for each question and the following variables of interest: professional category (nurses and nursing assistants and licensed practical nurses) and regions of Brazil (South, Southeast, Midwest, Northeast, and North). To assess knowledge of HH and calculate a total score, the Positivity Index (PI) was employed as an interpretive approach, considering the number of correct answers as indicators of positive outcomes. The PI was interpreted as follows: desirable (100% positivity); adequate (between 99% and 90% positivity); safe (between 89% and 80% positivity); borderline (between 79% and 71% positivity); and poor (70% or less positivity).[23,24] Thus, one point was assigned for each correct question regarding professionals' knowledge of HH; the final score was calculated by summing up the points obtained; and a percentage was assigned and categorized according to the PI. To examine the relationship between the positivity level and professional category, the Adequate and Safe indices were combined, while the Borderline and Poor indices were grouped together. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 23 software.

Ethical Aspects

This study received approval from the Research Ethics Committee of the *Escola de Enfermagem de Ribeirão Preto*, *Universidade de São Paulo* (REC-EERP/USP), with Certificate of Presentation for Ethical Consideration (CAAE - *Certificado de Apresentação para Apreciação Ética*) n° 38623520.6.0000.5393 and Protocol number 4381042 approved on November 5, 2020. All participants were informed about the purposes and methods used in the study, emphasizing their right to withdraw from the research at any time. The research was conducted following the ethical standards required - Resolutions 466/2012, 510/2016 and 580/2018 from the Ministry of Health.

RESULTS

Sociodemographic data were collected from 493 nursing professionals from all regions of Brazil who completed the Google Forms® questionnaire. The majority of the sample was from São Paulo state (330/66.8%), followed by Rio de Janeiro state (46/9.3%), representing predominantly the Southeast region (74.6%). Regarding institutional profiles, most professionals worked at general hospitals (219/44.3%), followed by home care services (47/9.5%), emergency units (45/9.1%), and university hospitals (44/8.9%). Concerning gender composition, the majority of participants were female (75.8%). Regarding employment status, most participants held a single job (392/79.4%), while 4% had three simultaneous nursing jobs. It was observed that only in the South and North regions were there more licensed practical nurse than nurses (Table 1).

Table 2 presents the absolute frequency (n) and relative frequency (%) of correct answers to the HH knowledge questionnaire by nursing professionals in the five regions of Brazil, grouped by professional category, and Fisher's exact test was performed to verify the association between correct answers and professional category. Regarding the minimum time to destroy microorganisms on hands, 65.6% of professionals answered correctly, and it is important to highlight that there was a significant difference between the correct answer and professional category, with 69.6% of nurses answering correctly compared to 55.6% of nursing assistants and licensed practical nurses. As for the regions of Brazil, when performing the chi-square test, no significant difference was found in professionals' correct answers regarding HH knowledge. Of correct answers regarding the type of HH required in different situations by nursing professionals in the five regions of Brazil, grouped by professional category, and the association between correct answers and professional category. A difference was observed between nurses and nursing assistants and licensed practical nurses in their answers regarding the type of HH required before writing in patients' medical records (p=0.004), before patient contact (p=0.018), upon returning to the unit after lunch (p=0.002), when leaving patients (p=0.004), and after visible blood exposure (p=0.006), which are highlighted in the table with an asterisk (*).

In the chi-square test, there was only an association found between the correct answers and the different regions of Brazil regarding surfaces that can become contaminated with microorganisms and transfer them to patients if hands are not properly sanitized before contact. In the question regarding intact skin of another patient (p=0.029), 60% of professionals from the North region answered "no" while 88.2% of professionals from the Southeast region answered "yes". In the question regarding the patients themselves (p=0.048), a significant difference was also observed as well as in the question about the bedside table of another patient (p=0.016). No significant difference was found between the correct answers and the different professional categories. Table 3 presents the correct answers of nursing professionals with the association between professional categories (nurses and nursing assistent/licensed practical nurse) regarding the use of alcohol-based hand rub and HH.

In figure 1, a total score of correct answers regarding knowledge of HH was assigned, and the correct answers were grouped by professional and classified according to the PI. No professional was classified as desirable (100%), while only 4 professionals were classified as adequate (between 99% and 90%). The majority of professionals (74.7%) were classified as borderline or poor in terms of knowledge of HH.

Table 1. Absolute (n) and relative (%) sociodemographic characterization of the total sample and grouped by professional category and regions of Brazil.

Variables	General n (%)	Professional Category N (%)		Regions of Brazil N (%)				
		NURSE	TECH	South	Southeast	Midwest	Northeast	North
1. Gender								
Female	374 (75.8)	267 (74.6)	107 (79.3)	20 (80.0)	297 (74.6)	22 (78.6)	32 (86.5)	3 (60.0)
Male	119 (24.2)	91 (25.4)	28 (20.7)	5 (20.0)	101 (25.4)	6 (21.4)	5 (13.5)	2 (40.0)
2. Age group								
18 to 24	105 (21.3)	79 (22.1)	26 (19.3)	7 (28.0)	89 (22.4)	3 (10.7)	5 (13.5)	1 (20.0)
25 to 29	109 (22.2)	93 (26.0)	16 (11.9)	5 (20.0)	82 (20.6)	10 (35.7)	12 (32.4)	1 (20.0)
30 to 39	157 (31.8)	118 (33.0)	39 (28.9)	7(28.0)	127 (31.9)	11 (39.3)	11 (29.7)	2 (40.0)
40 to 49	100 (20.2)	57 (15.9)	43 (31.9)	5 (20.0)	85 (21.4)	3 (10.7)	5 (13.5)	1 (20.0)
50 to 59	22 (4.5)	11 (3.1)	11 (8.1)	1 (4.0)	15 (3.8)	1 (3.6)	4 (10.8)	1 (20.0)
3- Level of education								
Elementary school (9th year)	2 (0.4)	0 (0.0)	2 (1.5)	0 (0.0)	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
High school or secondary school	94 (19.0)	2 (0.6)	92 (68.1)	12 (48.0)	71 (17.7)	3 (10.7)	6 (16.2)	2 (40.0)
Higher education, teaching or bachelor's degree	148 (30.0)	112 (31.3)	36 (26.7)	3 (12.0)	128 (32.2)	7 (25.0)	9 (24.3)	1 (20.0)
Graduate, masters or doctoratal degrees	249 (50.4)	244 (68.2)	5 (3.7)	10 (40.0)	197 (49.5)	18 (64.3)	22 (59.5)	2 (40.0)
4- Number of workplaces								
1	392 (79.4)	289 (80.7)	103 (76.3)	20 (80.0)	318 (19.9)	22 (78.6)	27 (73.0)	5 (100)
2	81 (16.4)	55 (15.4)	26 (19.3)	4 (16.0)	66 (16.6)	5 (17.9)	6 (16.2)	0 (0.0)
3	20 (4.0)	14 (3.9)	6 (4.4)	1 (4.0)	14 (3.5)	1 (3.6)	4 (10.80)	0 (0.0)
5. Nature of the institution								
Public	195 (39.5)	145 (40.5)	50 (37)	9 (36.0)	156 (39.2)	8 (28.6)	19 (51.4)	3 (60.0)
Private	245 (49.6)	182 (50.8)	63 (46.7)	9 (36.0)	204 (51.3)	17 (60.7)	13 (35.1)	2 (40.0)
Public, private	53 (10.7)	31 (8.7)	22 (16.3)	7 (28.0)	38 (9.5)	3 (10.7)	5 (13.5)	0 (0.0)
6. Length of service (in years)								
< 1	118 (23.9)	97 (27.1)	21 (15.6)	1 (4.0)	95 (23.9)	9 (32.1)	12 (32.4)	1 (20.0)
Between 1 to 2	75 (15.2)	52 (14.5)	23 (17.0)	4 (16.0)	61 (15.3)	4 (14.3)	6 (16.2)	0 (0.0)
Between 3 to 4	60 (12.1)	42 (11.7)	18 (13.3)	6 (24.0)	44 (11.1)	7 (25.0)	3 (8.1)	0 (0.0)
Between 5 to 6	34 (6.9)	29 (8.1)	5 (3.7)	2 (8.0)	29 (7.3)	0 (0.0)	3 (8.1)	0 (0.0)
Between 7 to 8	34 (6.9)	23 (6.4)	11 (8.1)	2 (8.0)	27 (6.8)	3 (10.7)	2 (5.4)	0 (0.0)
Between 9 to 10	43 (8.7)	28 (7.8)	15 (11.1)	1 (4.0)	38 (9.5)	2 (7.1)	1 (2.7)	1 (20.0)
Between 11 to 15	45 (9.1)	31 (8.7)	14 (10.4)	5 (20.0)	35 (8.8)	1 (3.6)	3 (8.1)	1 (20.0)
Between 16 to 20	42 (8.5)	31 (8.7)	11 (8.1)	3 (12.0)	36 (9.0)	0 (0.0)	1 (2.7)	2 (40.0)
Between 21 to 30	40 (8.1)	25 (7.0)	15 (11.1)	1 (4.0)	31 (7.8)	2 (7.1)	6 (16.2)	0 (0.0)
≤ 31	2 (0.4)	97 (27.1)	2 (1.5)	1 (4.0)	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
7. Profession								
Nurse	-	-	-	10 (40.0)	291 (73.1)	24 (85.7)	31 (83.8)	2 (40.0)
Licensed practical nurse				15 (60.0)	82 (20.6)	4 (14.3)	6 (16.2)	3 (60.0)
Nursing assistant				0 (0.0)	25 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)

Source: authors' data. TECH = nursing assistants and licensed practical nurses.

Table 2. Absolute (n) and relative (%) frequency of correct answers to the hand hygiene knowledge questionnaire by nursing professionals in the five regions of Brazil, grouped by professional category and association between correct questions and professional category. Brazil, 2023.

	General n (%)	Regions of Brazil N (%)					Professional Category N (%)		
Variables		**South**	**Southeast**	**Midwest**	**Northeast**	**North**	**NURSE**	**TECH**	***P***
Have you received any training in hand hygiene?									
Yes	472 (95.5)	24 (96.0)	380 (95.5)	28 (100)	35 (94.6)	5 (100)	341 (95.3)	131 (97.0)	-
No	21 (4.3)	1 (4.0)	18 (4.5)	0 (0.0)	2 (5.4)	0 (0.0)	17 (4.7)	4 (3.0)	
Is there an alcoholic preparation available for hand hygiene in your institution?									
Yes	475 (96.2)	24 (96.0)	382 (96)	28 (100)	36 (97.3)	5 (100)	345 (96.4)	130 (96.3)	-
No	18 (3.6)	1 (4.0)	16 (4.0)	0 (0.0)	1 (2.7)	0 (0.0)	13 (3.6)	5 (3.7)	
Which of the following is the main route of cross-transmission of potentially pathogenic microorganisms between patients in health care settings?									
Health professionals' hands when they are not sanitized	441 (89.3)	20 (80.0)	357 (89.7)	26 (92.9)	34 (91.9)	4 (80.0)	326 (91.1)	115 (85.2)	0.070
What is the most frequent source of microorganisms responsible for healthcare-associated infections?									
Microorganisms already present on or near patients	160 (32.4)	4 (16.0)	130 (32.7)	14 (50.0)	12 (32.4)	0 (0.0)	115 (32.1)	45 (33.3)	0.829
What is the minimum time required for the alcoholic preparation to destroy most microorganisms on your hands?									
20 seconds	324 (65.6)	17 (68.0)	259 (65.1)	21 (75.0)	26 (70.3)	1 (20.0)	249 (69.6)	75 (55.6)	0.004*
Which of the following statements about hand hygiene techniques are true? Alcoholic preparation should cover all surfaces of both hands.									
True	480 (97.2)	25 (100)	387 (97.2)	27 (96.4)	36 (97.3)	5 (100)	348 (97.2)	132 (97.8)	0.771
Hands must be dry before use.									
True	451 (91.3)	23 (92.0)	362 (91.0)	28 (100)	33 (89.2)	5 (100)	332 (92.7)	119 (88.1)	0.146
You can dry your hands with a paper towel after rubbing your hands with the alcoholic preparation.									
False	426 (86.2)	19 (76.0)	346 (86.9)	26 (92.9)	32 (86.5)	3 (60.0)	319 (89.1)	107 (79.3)	0.769
What type of hand hygiene is needed in the following situations? a. Before writing in the patient's record									
Rubbing alcohol	321 (65.0)	11 (44.0)	263 (66.1)	20 (71.4)	26 (70.3)	1 (20.0)	247 (69.0)	74 (54.8)	0.004*
B. Before patient contact									
Rubbing alcohol	196 (39.7)	9 (36.0)	161 (40.5)	14 (50.0)	12 (32.4)	5 (100)	154 (43.0)	42 (31.1)	0.018*
C. Arriving at the unit after lunch									
Water and soap	393 (79.6)	21 (84.0)	314 (78.9)	22 (78.6)	31 (83.8)	0 (0.0)	273 (76.3)	120 (88.9)	0.002*
D. Before giving an injection									
Rubbing alcohol	237 (48.0)	11 (44.0)	194 (48.7)	16 (57.1)	14 (37.8)	2 (40.0)	175 (48.9)	62 (45.9)	0.613
E. Before emptying the urinal									
Rubbing alcohol	256 (51.8)	10 (40.0)	209 (52.5)	19 (67.9)	16 (43.2)	2 (40.0)	192 (53.6)	64 (47.4)	0.227
F. Before opening the patient's room door									
Rubbing alcohol	378 (76.5)	16 (64.0)	308 (77.4)	22 (78.6)	28 (75.7)	4 (80.0)	273 (76.3)	105 (77.8)	0.811
G. After giving an injection									
Water and soap	290 (58.7)	209 (58.4)	81 (60.0)	18 (72.0)	229 (57.5)	16 (57.1)	23 (62.2)	4 (80.0)	0.759
H. After emptying the urinal									
Water and soap	404 (81.8)	21 (84.0)	324 (81.4)	24 (85.7)	31 (83.8)	4 (80.0)	289 (80.7)	115 (85.2)	0.294
I. After removing procedure gloves									
Water and soap	361 (73.1)	21 (84.0)	283 (71.1)	21 (75.0)	32 (86.5)	4 (80.0)	256 (71.5)	105 (77.8)	0.161
J. When leaving the patient									
Rubbing alcohol	205 (41.5)	8 (32.0)	171 (43.0)	12 (42.9)	13 (35.1)	1 (20.0)	163 (45.5)	42 (31.1)	0.004*
K. After making the patient's bed									
Rubbing alcohol	214 (43.3)	8 (32.0)	184 (46.2)	11 (39.3)	11 (29.7)	5 (100)	169 (47.2)	45 (33.3)	0.006*
L. After visible exposure to blood									
Water and soap	447 (90.5)	22 (88.0)	363 (91.2)	26 (92.9)	32 (86.5)	4 (80.0)	329 (91.9)	118 (87.4)	0.163
M. After contact with a patient with diarrhea									
Water and soap	451 (91.3)	24 (96.0)	361 (90.7)	27 (96.4)	34 (91.9)	0 (0.0)	328 (91.6)	123 (91.1)	1,000
N. Before bed disinfection after patient discharge									
Rubbing alcohol	189 (38.3)	7 (28.0)	157 (39.4)	13 (46.4)	11 (29.7)	1 (20.0)	148 (41.3)	41 (30.4)	0.029*

*Source: authors' data. TECH = Nursing Assistants and Licensed Practical Nurses; *significance level: p < 0.05.*

Table 3. Absolute (n) and relative (%) frequency of correct answers on knowledge about hand hygiene by nursing professionals, grouped by professional category and association between correct questions and professional category. Brazil, 2023.

Variables	Answer	General	NURSE n (%)	TECH n (%)	Z	*P*	OR	95% CI LI - LS
Which of the following items should be avoided because they are associated with the possibility of hand colonization?								
a. Jewelry use	Yes	478	350 (97.8)	128 (94.8)	2.893	0.136	2.393	0.850 - 6.731
b. Damaged skin	Yes	450	330 (92.2)	120 (88.9)	1.333	0.283	1.473	0.761 - 2.853
c. Artificial/false nails	Yes	474	345 (96.4)	129 (95.6)	0.175	0.793	1.234	0.459 - 3.316
d. Regular use of a hand cream	No	218	162 (45.3)	56 (41.5)	0.565	0.478	0.858	0.575 - 1.280
Antiseptic hand rub with alcohol-based hand rub and hand hygiene with soap and water are true?								
a. Rubbing your hands with an alcoholic preparation is faster than cleaning them with soap and water	True	342	255 (71.2)	87 (64.4)	2.124	0.155	1.366	0.897 - 2.079
b. Rubbing your hands with an alcoholic preparation dries out your skin more than washing your hands with soap and water.	True	398	282 (78.8)	116 (85.6)	3.226	0.075	0.608	0.352 - 1.050
c. Rubbing your hands with an alcoholic preparation is more effective against microorganisms than cleaning them with soap and water	False	402	297 (83.0)	105 (77.8)	1.750	0.194	0.719	0.440 - 1.174
Which of the following hand hygiene actions prevent cross-transmission of microorganisms to the patient?								
a. Hand hygiene before patient contact	Yes	492	357 (72.6)	135 (27.4)	0.378	1.000	-	-
b. Hand hygiene after patient contact	Yes	488	355 (72.7)	133 (27.3)	0.404	0.618	1.779	0.294 - 10.768
c. Hand hygiene immediately after body fluid exposure risk	Yes	485	354 (73.0)	131 (27.0)	2.092	0.223	2.702	0.666 - 10.962
d. Hand hygiene after exposure to surfaces and objects close to the patient	Yes	474	346 (73.0)	128 (27.0)	0.889	0.430	1.577	0.607 - 4.093
Which of the following hand hygiene actions prevent the patient from becoming infected with their own microorganisms?								
a. Hand hygiene before patient contact	No	1	1 (0.3)	0 (0.0)	3.357	0.094	0.443	0.182 - 1.081
b. Hand hygiene after patient contact	No	5	3 (0.8)	2 (1.5)	0.009	1.000	1.040	0.469 - 2.309
c. Hand hygiene immediately after body fluid exposure risk	Yes	485	354 (98.9)	131 (97.0)	0.333	0.593	1.341	0.493 - 3.648
d. Hand hygiene immediately before performing an aseptic procedure	Yes	474	346 (96.6)	128 (94.8)	0.398	0.611	0.698	0.228 - 2.142
Which of the following hand hygiene actions prevent healthcare worker infection?								
a. Hand hygiene after patient contact	Yes	453	324 (90.5)	129 (95.6)	0.378	1,000	-	-
b. Hand hygiene immediately after body fluid exposure risk	Yes	461	335 (93.3)	126 (93.3)	1.138	0.565	-	-
c. Hand hygiene immediately before performing an aseptic procedure	No	18	12 (3.4)	6 (4.4)	2.119	0.158	0.602	0.302 - 1.200
d. Hand hygiene after exposure to surfaces and objects close to the patient	Yes	474	343 (95.8)	131 (97.0)	0.456	0.503	1.531	0.441 - 5.316
Which of the following surfaces could contaminate your hands with microorganisms that you could transfer to patients if you don't sanitize them before touching them?								
a. Patients' room door handle	Yes	492	358 (100)	134 (99.3)	2.657	0.274	-	-
b. Patients' own bedding	Yes	423	304 (84.9)	119 (88.1)	0.841	0.389	0.757	0.417 - 1.375
c. Another patient's intact skin	Yes	432	321 (89.7)	111 (82.2)	5.008	0.031	1.876	1.075 - 3.275
d. Patients' own intact skin	Yes	346	254 (70.9)	92 (68.1)	0.368	0.581	1.142	0.744 - 1.751
e. Patients' record	Yes	418	319 (89.1)	99 (73.3)	18.908	0.000	2.974	1.793 - 4.933
f. The walls of the patients' room	Yes	425	313 (87.4)	112 (83.0)	1.645	0.241	1.428	0.827 - 2.468
g. Another patient's bedside table	Yes	474	346 (96.6)	128 (94.8)	0.889	0.430	1.577	0.607 - 4.093

*Source: authors' data. TECH = nursing assistants and licensed practical nursea; *significance level: p < 0.05*

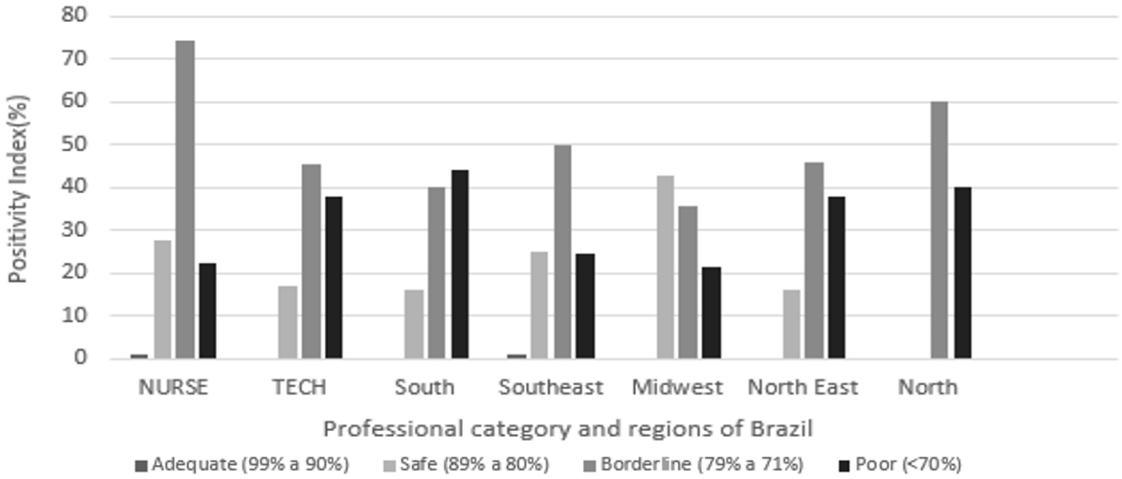

Figure 1. Positivity Index about knowledge about Hand Hygiene. Brazil, 2023.

In figure 2, adequate and safe PI (between 99% and 80%) were grouped together, while borderline and poor groups (<79%) were grouped separately to verify the association between professional categories and visualize where significant differences occurred. The graph reveals that nurses had a higher PI between adequate and safe compared to nursing assistents and licensed practical nurses, while the latter category had a higher index in borderline and poor groups. When checking the association between regions and grouping (adequate/safe and borderline/poor), only the Southeast region showed an association [X^2=6.258 (1); p=0.014].

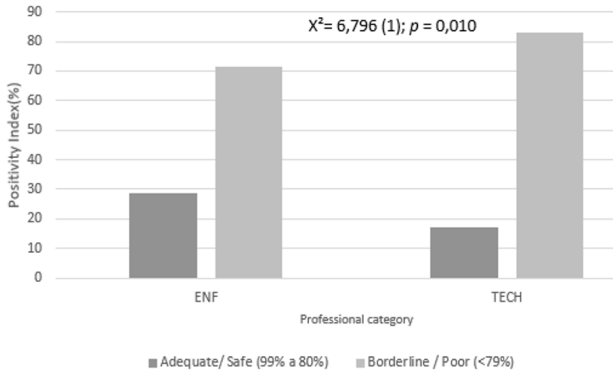

Figure 2. Positivity Index about knowledge about hand hygiene among professional categories (nurses/nursing assistants and licensed practical nurses (TECH)). Brazil, 2023.

DISCUSSION

Our aim was to assess nursing professionals' knowledge regarding HH during the COVID-19 pandemic. These professionals reported receiving training on HH, and the institution provided hand sanitizer for practice. Although a minority correctly identified the most common source of infection-related microorganisms, the majority understood the minimum time required to eliminate these microorganisms from hands. When examining the association between this knowledge, professional categories, and regions in Brazil, significant differences were noted: nurses provided more correct answers compared to nursing assistants and licensed practical nurses. However, regions in Brazil showed no association with correct answers. While most professionals acknowledge the importance of HH, there were statistically significant differences in understanding the type of hygiene needed in different situations, especially before patient contact, upon arrival at the unit after lunch, before leaving the patient, and after visible blood exposure.

Regarding questions about contamination routes, there was no association between correct answers and professional categories. When analyzing the total score of correct answers on HH knowledge, scores were grouped using the PI. No professional was classified as desirable, and the majority fell into the borderline or poor categories. Although there were no significant differences between Brazilian regions, a notable association was observed among professional categories. Nurses demonstrated a higher adequate and safe PI compared to nursing assistants and licensed practical nurses, who showed higher ratings in borderline and poor categories. These outcomes highlight the need for nursing professionals to enhance their overall understanding of HH, including knowledge of common sources of HAI and appropriate HH practices in diverse scenarios. HH remains one of the most effective and cost-efficient strategies for controlling HAI, requiring correct application, especially during pandemics and at all times. [3,13,25]

HH is one of the key pillars in HAI prevention and control and crucial to prevent HAI and reduce their potential impact. Nursing professionals play a vital role in preventing the spread of infections through their compliance with HH practices.[3,13,25] Therefore, it is essential for nursing professionals to have knowledge about infection prevention and control measures, especially regarding HH.[26–28] However, despite the importance of this issue, many professionals still do not believe in the effectiveness of these measures, which can result in failures in implementing preventive practices. Therefore, it is im-

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portant to invest in ongoing training for nursing professionals and promote a patient safety culture. Regarding the minimum time required for antiseptic hand rubbing, 65.6% of professionals answered correctly about the time needed to destroy the majority of microorganisms with alcohol-based preparations. Although a study reported that participants stated that one minute was necessary for this HH procedure,[28] it is important to highlight that one minute is not the recommended minimum time. Additionally, a significant difference was found in the answers about the minimum rubbing time with alcohol--based preparations and whether hand drying can be done after rubbing with alcohol-based preparations between nurses and licensed practical nurses, indicating that higher-level professionals have a more solid theoretical foundation in this area.[28,29]

Although the majority of licensed practical nurses answered correctly, many professionals, regardless of professional category or region in Brazil, still believe that the most frequent source is the hospital environment, rather than the patient and their surroundings. This indicates the need for guidance and monitoring of nurses regarding HH practices for the healthcare staff, patients, and family members.[28,30–32] Many professionals report performing HH with soap and water when they could be using alcohol-based hand rub. The knowledge gap regarding the use of alcohol-based preparations can be justified by the fact that simple handwashing with soap and water is still the preferred method among healthcare professionals.[33,34] However, it is important to highlight that, during the COVID-19 pandemic, the use of alcohol--based products was strongly encouraged everywhere, especially in healthcare settings.[33,34] It is worth noting that different regions of Brazil have their own cultural peculiarities. However, it is crucial to emphasize that HH protocols and recommendations are adopted based on both national and international guidelines. Regarding HH training, it is noteworthy that the vast majority of professionals reported having received training on this topic.[29,31,35]

The COVID-19 pandemic has brought to light the importance of HH as a preventive measure to avoid the spread of infectious diseases. However, studies conducted during the pandemic have shown the need for approaches to improve nursing professionals' knowledge about HH.[12,36,37] A study conducted in an Adult Intensive Care Unit before the COVID-19 pandemic revealed that, after providing care, the moment when professionals performed HH the most was when they had contact with patients, prioritizing only their own safety.[38] This highlights the need to implement strategies for HH, such as easy access to alcohol-based preparations and other supplies intended for this purpose, professional education, visual re-minders in strategic locations, and monitoring of HH practices with performance feedback to professionals. These actions are likely to improve overall compliance with practice. The World Health Organization has developed an electronic guide for implementing the multimodal strategy to improve HH, which includes key elements such as staff instruction and motivation programs, adoption of alcohol-based products as the gold standard, use of performance indicators, and strong commitment from all stakeholders, including frontline staff, managers, and healthcare leaders.[39] It is important to note that, despite 95.5% of participants in the studies having received HH training, there are knowledge gaps in this topic among the investigated staff. This indicates the need to encourage measures aimed at improving compliance with HH, especially in future situations that may require similar preventive measures. It is essential for nursing professionals to have a comprehensive understanding of the importance of HH as one of the primary measures against HAI, with a particular emphasis on pandemics.[12,29,36,38]

The study in question points to the need for intensifying educational strategies and monitoring indicators to enhance nursing staff's knowledge and ensure proper HH implementation. When it comes to general knowledge about HH, no nursing professional was classified as desirable, and only a very small percentage was considered adequate. Based on the results obtained in recent studies, there is a clear need to expand nursing staff's knowledge regarding HH and, consequently, improve the proper implementation of this practice.[27,30,34,35] Nurses demonstrated more adequate knowledge compared to nursing assistants and licensed practical nurses. The longer training duration and the ongoing demands within the nursing profession may have contributed to their enhanced understanding. This highlighting the importance of nurses' leadership in the staff, always encouraging and teaching the staff about the most current and appropriate protocols.[40]

The assessment of nursing professionals' knowledge about HH is of utmost importance to ensure patient safety, especially during pandemics like the case of COVID-19. In this regard, our research conducted in all regions of Brazil revealed a knowledge that is borderline to poor, even though there is a low representativeness of the regions, the sample is heterogeneous. Although using a self-assessment questionnaire at a time when there were incentives, investments, fear, and motivation for HH showed a knowledge far below the desirable, indicating a concern in other moments when HH is not as evident.[41,42] We can have a snapshot of professionals' reality in Brazil during the pandemic, which was a delicate and important period for controlling HAI, especially COVID-19. Thus, it is crucial for healthcare professionals to be properly trained and aware of the importance of HH in preventing disease transmission. Studies like this can provide valuable information for implementing patient safety policies and practices in hospitals and healthcare units worldwide as well as healthcare professional safety, especially during pandemics.[43,44]

Some limitations should be considered when interpreting our results, such as convenience sample, online data collection, and the specific context of the study. However, it provides significant contributions to HH, with valuable insights for nursing professionals and a basis for interventions and policies. The findings encourage future

research on the effectiveness of HH in preventing HAI.

Considering the presented results, it is possible to conclude that the training of nursing professionals regarding HH should be continuous and assessed in order to ensure the desired knowledge of HH protocols and reduce the risk of HAI. It is necessary to recognize that the nursing staff plays a crucial role in promoting HH not only for themselves but also for the community at large. Therefore, investments in training and awareness should be prioritized to ensure patients and healthcare professional safety at all times, with even greater emphasis during pandemics.

Nursing professionals, in general, have a limited and poor knowledge of HH. It is important to note that there are differences among professional categories and in some aspects across regions in Brazil. The nursing staff should be constantly trained and guided in infection control and prevention, raising awareness about the importance of HH knowledge in crucial moments such as pandemics, as Florence Nightingale already emphasized in the early days of nursing, to ensure the quality of healthcare, prevent HAI, and ensure healthcare professional safety. This analysis will enable the development of more accurate and effective strategies for improving HH knowledge and practice, thereby reducing the spread of SARS-CoV-2 and other pathogens.

Additionally, to enhance the knowledge and practice of HH among nursing professionals, it is essential to provide specific recommendations. This may include implementing educational programs, practical training sessions, regular assessments, and feedback mechanisms. Emphasizing the impact on patient safety is crucial, highlighting the consequences of inadequate HH practices, such as increased rates of HAI, patient morbidity and mortality, and the economic burden on healthcare systems. Connecting with global initiatives and guidelines, such as the World Health Organization's "My 5 Moments for Hand Hygiene" approach, reinforces the importance of addressing the identified knowledge gaps. By aligning the study's findings with internationally recognized standards, the conclusion emphasizes the urgency of improving knowledge and HH practices.

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AUTHORS' CONTRIBUTIONS

Jéssica Fernanda Corrêa Cordeiro contributed to the project administration, bibliographical research, writing the summary, introduction, methodology, discussion, interpretation and description of results, preparation of tables, conclusions, review, statistics and final approval of the version to be published. **Daniella Corrêa Cordeiro** contributed to project administration, bibliographical research, writing the summary, introduction, methodology, discussion, interpretation and description of results, preparation of tables, conclusions, review, statistics and final approval of the version to be published. **Ludmila Albano de Felice Gomes** contributed to the bibliographical research, writing the summary, discussion, interpretation and description of the results, conclusions, review and final approval of the version to be published. Tatiana Areas da Cruz contributed to project administration, review and final approval of the version to be published. **Marilia Duarte Valim** contributed to project administration, review and final approval of the version to be published. **Denise de Andrade** contributed to the administration and supervision of the project, interpretation of results, review and final approval of the version to be published. **André Pereira dos Santos** contributed to project administration, bibliographical research, writing the summary, introduction, methodology, discussion, interpretation and description of results, preparation of tables, conclusions, review, statistics and final approval of the version to be published.

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ORIGINAL ARTICLE

Mortality trend due to HIV/AIDS among women in Porto Alegre/RS from 2007 to 2017

Tendência de mortalidade por HIV/AIDS entre mulheres em Porto Alegre/RS de 2007 a 2017

Tendencia de mortalidad por VIH/SIDA entre mujeres en Porto Alegre/RS de 2007 a 2017

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Corresponding Author:
Maiton Bernardelli
bernardelli.maiton@gmail.com

Addresss: Avenida Sirius, 92, Bairro Cruzeiro, Caxias do Sul/RS.

Maiton Bernardelli[1];
Douglas Nunes Stahnke[2];
Tonantzin Ribeiro Gonçalves[3];
Marcos Pascoal Pattussi[2];

[1] Centro Universitário da Serra Gaúcha - FSG. Caxias do Sul, RS, Brazil.
[2] Universidade do Vale do Rio dos Sinos (Unisinos), Graduate Program in Public Health, São Leopoldo, RS, Brazil.
[3] Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA), Porto Alegre, RS, Brazil.

ABSTRACT

Background and Objectives: Porto Alegre is among the state capitals of Brazil with the highest magnitude of epidemiological indicators in relation to people living with HIV/AIDS, impacting the mortality indicators of this population. This study aimed to analyze the temporal trend of deaths from HIV/AIDS in women residents of the city of Porto Alegre, Rio Grande do Sul, Brazil, from 2007 to 2017, considering age groups, skin color and education. **Method:** this is an ecological time series study on the trend of HIV/AIDS mortality rates among women living with HIV residents in the city of Porto Alegre, RS. Unadjusted and standardized mortality rates were calculated according to age group, skin color and education. For trend analysis, Prais-Winsten generalized linear regression was used. **Results:** 1,603 deaths related to HIV/AIDS were identified in women living in the city during the study period. Mortality coefficients were higher in white, less educated women, with an increasing trend among those over 60 years of age (95%CI 0.044; 0.029) with a decline for those in the age group between 20 and 29 (95%CI - 0.566; - 0.120). **Conclusion:** changes in the epidemiological scenario of HIV/AIDS draw attention to the care of people over 60 years of age and with less education, requiring efforts from healthcare networks to prevent deaths.

Keywords: *HIV. AIDS. Mortality. Women's Health.*

RESUMO

Jutificativa e Objetivos: Porto Alegre está entre as capitais estaduais do Brasil com maior magnitude de indicadores epidemiológicos em relação às pessoas vivendo com HIV/AIDS, impactando os indicadores de mortalidade dessa população. Este estudo teve como objetivo analisar a tendência temporal de mortes por HIV/AIDS em mulheres residentes na cidade de Porto Alegre, Rio Grande do Sul, Brasil, de 2007 a 2017, considerando grupos etários, cor da pele e educação. **Método:** trata-se de um estudo de série temporal ecológica sobre a tendência das taxas de mortalidade por HIV/AIDS entre mulheres vivendo com HIV residentes na cidade de Porto Alegre, RS. As taxas de

mortalidade não ajustadas e padronizadas foram calculadas de acordo com grupo etário, cor da pele e educação. Para análise de tendência, foi utilizada regressão linear generalizada de Prais-Winsten. **Resultados:** Foram identificadas 1.603 mortes relacionadas ao HIV/AIDS em mulheres residentes na cidade durante o período do estudo. Os coeficientes de mortalidade foram mais altos em mulheres brancas, menos escolarizadas, com uma tendência crescente entre aquelas com mais de 60 anos de idade (IC95% 0,044; 0,029) com declínio para aquelas na faixa etária entre 20 e 29 anos (IC95% -0,566; -0,120). **Conclusão:** Mudanças no cenário epidemiológico do HIV/AIDS chamam a atenção para o cuidado de pessoas com mais de 60 anos de idade e com menor escolaridade, exigindo esforços das redes de saúde para prevenir mortes.

Palavras-chave: *HIV. AIDS. Mortalidade. Saúde da Mulher.*

RESUMEN

Antecedentes y Objetivos: Porto Alegre está entre las capitales estatales de Brasil con la mayor magnitud de indicadores epidemiológicos en relación a las personas que viven con VIH/SIDA, impactando los indicadores de mortalidad de esta población. Este estudio tuvo como objetivo analizar la tendencia temporal de muertes por VIH/SIDA en mujeres residentes en la ciudad de Porto Alegre, Rio Grande do Sul, Brasil, de 2007 a 2017, considerando grupos de edad, color de piel y educación. **Método:** se trata de un estudio de serie temporal ecológica sobre la tendencia de las tasas de mortalidad por VIH/SIDA entre mujeres que viven con VIH residentes en la ciudad de Porto Alegre, RS. Se calcularon tasas de mortalidad no ajustadas y estandarizadas según grupo de edad, color de piel y educación. Para el análisis de tendencia, se utilizó la regresión lineal generalizada de Prais-Winsten. **Resultados:** Se identificaron 1.603 muertes relacionadas con el VIH/SIDA en mujeres residentes en la ciudad durante el período de estudio. Los coeficientes de mortalidad fueron más altos en mujeres blancas, menos educadas, con una tendencia creciente entre aquellas con más de 60 años de edad (IC95% 0,044; 0,029) con un declive para aquellas en el grupo de edad entre 20 y 29 años (IC95% -0,566; -0,120). **Conclusión:** Los cambios en el escenario epidemiológico del VIH/SIDA llaman la atención sobre el cuidado de las personas mayores de 60 años y con menor educación, requiriendo esfuerzos de las redes de salud para prevenir muertes.

Palabras clave: *VIH. SIDA. Mortalidad. Salud de la Mujer.*

INTRODUCTION

The increase in the number of Human Immunodeficiency Virus (HIV) infections is considerable in Brazil,[1] even though public actions and policies have expanded strategies aimed at reducing virus transmission, based on the implementation of universal access to antiretroviral therapy (ART) by the Brazilian Health System in 1996.[2] In recent years, there has been an increase in the number of Acquired Immune Deficiency Syndrome (AIDS) cases in women[3,4] and, especially, in contexts of high HIV prevalence. Mortality due to AIDS, or its complications, has intensified, affecting especially women in greater social vulnerability.[5] AIDS-related illnesses are the second leading cause of death among young women aged 15 to 24 years in African countries, and continue to be the leading causes of death among women of reproductive age (15-49 years) worldwide.[6]

In 2017, 49% of cases of death due to AIDS in Brazilian women fell within the age group of 25 to 39 years of age.[3] The capital of the state of Rio Grande do Sul, Porto Alegre, stands out for a persistent growth in AIDS-related mortality rates among women living with HIV (WLWHIV), especially among those with greater social vulnerability.[5] In the city of Porto Alegre, capital of the state of Rio Grande do Sul, characterized by the predominance of the female population in the age group from 20 to 29 years, there is a high incidence of HIV cases in relation to the country, with a 4% increase in the absolute number of deaths of women of childbearing age in 2017 compared to the previous year.[7] Diseases caused by HIV alone accounted for 17% of total deaths of women of childbearing age in the same period, compared to what was found in the city for 2016. This persistent growth in AIDS-related mortality rates among WLHIV has been identified since 2007 and reflected in a mortality rate of 2.7% (95%CI 1.8 - 3.5)[4] among WLHIV residing in the capital of Rio Grande do Sul between 2000 and 2011.[4] Increasing this increase, for 2018, a coefficient of 24.2 deaths/100 thousand inhabitants was recorded, exceeding the national AIDS mortality rate by five times.[8]

Most epidemiological studies that focus on the issue of WLWHIV mortality highlight HIV/AIDS as the main cause, however, they only present indicators of mortality in women of childbearing age or in pregnant and postpartum women, focusing on maternal mortality.[9] The lack of epidemiological indicators that cover all WLWHIV represents one of the challenges in combating the epidemic, especially as it is not possible to capture health inequities and the impact of late diagnosis. Studies that encourage the production of accurate information on morbidity and mortality can favor evidence-based strategies focused on preventing deaths of people living with HIV (PLWHIV),[10] contributing to mitigating barriers to monitoring and assessing local responses to the epide-

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mic. Therefore, this study aimed to analyze deaths from HIV/AIDS in women living in the city of Porto Alegre, Rio Grande do Sul, Brazil, from 2007 to 2017, considering age groups, skin color and education.

METHODS

This is an ecological time series study on the trend in HIV/AIDS mortality rates among WLHIV living in the city of Porto Alegre, RS. The study population was made up of all women living in the city who died from HIV/AIDS between 2007 and 2017. We used death data from the Mortality Information System (SIM), provided by the Municipal Health Secretariat of the City Hall of Porto Alegre/RS (MHD/POA), which stores digital data from the Death Certificate (DC) including the cause of death.

To calculate mortality rates per 100 thousand inhabitants, all deaths of women whose causes were classified as related to HIV/AIDS (B20-24), according to the codes of the 10th Revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10), were included. The remaining death cases were excluded from the database. Deaths in children under fifteen years of age were excluded from the analyzes due to the low number of deaths (n=13). Unadjusted mortality rates were calculated according to age group, skin color and education. The standardization of HIV/AIDS mortality rates by age was carried out in all years of the studied period, using the direct method in which specific coefficients from the standard population were applied to the populations under study, estimating the number of deaths expected if the populations had the same coefficients as the standard population. The information on the resident population used in calculating mortality rates corresponds to data estimated by the Brazilian Institute of Geography and Statistics (IBGE - *Instituto Brasileiro de Geografia e Estatística*).

Data were analyzed according to sociodemographic variables, such as age group in years (15-19, 20-29, 30-39, 40-49, 50-59 and 60 years and older), skin color (white, black/brown, yellow) and education (no education/incomplete elementary school, complete elementary school/incomplete high school, complete high school/incomplete higher education and complete higher education), according to the IBGE Census classification for 2010. For trend analysis, Prais-Winsten generalized linear regression was used, in which the independent variables (X) were the years in which deaths occurred and mortality rates were considered dependent variables (Y). Trends were classified according to the direction of their regression coefficients and statistical significance values as: - increasing (p-value <0.05 and positive coefficient); - negative (p-value <0.05 and negative coefficient); - or stable (p-value>0.05). For the analyses, SPSS 20.0 and Stata 12 were used.

This study is part of a larger study entitled "Space-time indicators and risk factors associated with mortality in women living with HIV", which was conducted in accordance with the required ethical standards, according to Resolutions 466/2012, 510/2016 and 580/2018 from the Ministry of Health, approved by the Research Ethics Committees (REC) of the *Universidade do Vale do Rio dos Sinos* (Unisinos) [REC/Unisinos: Opinion 3.233.242, approved on March 29, 2019; Certificate of Presentation for Ethical Consideration (CAAE - *Certificado de Apresentação para Apreciação Ética*) 06210919.7.0000.5344] and the Porto Alegre Municipal Health Department (REC/SMSPA: Opinion 3.281.948, approved on April 24, 2019; CAAE 06210919.7.3001.5338).

RESULTS

Among the 61,644 deaths of women living in the city of Porto Alegre, in the period between 2007 and 2017, there were 1,603 related to HIV/AIDS, with a predominance of deaths among those in the age group of 30 to 39 years (29.7%), of brown skin color (53.6%) and with complete elementary school and incomplete high school (25.3%) (Table1).

Table 1. Sociodemographic characteristics of women living with HIV living in Porto Alegre who died from HIV/AIDS between 2007 and 2017 (n=1,603, MHD/POA).

	N	%
Age	15	0.9
15-19 years	217	13.5
20-29 years	476	29.7
30-39 years	453	28.3
40-49 years	269	16.8
50-59 years	158	9.9
60 years and older		
Skin color	859	53.6
White	495	30.9
Black/brown	215	13.4
Yellow		
Education[a]	9	0.6
No education/incomplete elementary school	405	25.3
Complete elementary school/incomplete high school	499	31.1
Complete high school/incomplete higher education	183	11.4
Graduated		

[a] *According to IBGE classification, 2010.*

A slight decrease in mortality rates due to HIV/AIDS in women living in Porto Alegre was observed between the first and last period; however, a rate of 10.41 deaths per 100 thousand women was recorded in 2010 among those aged 30 to 39 years old. However, at the end of the period, the highest coefficient found was among women aged 40-49 years, with 7.32 deaths per 100 thousand women (Table 2).

Despite the increase in overall AIDS mortality rates in WLHIV until 2010 (6.6 deaths/1.000 inhabitants), a continued decline was observed at the end of the period analyzed. However, the downward trend in coefficients (95%CI: -0.307; 0.019) did not present statistical significance.

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Table 2. Mortality coefficients due to HIV/AIDS in women aged 15 or over, standardized and specific, by year of occurrence and age group, in Porto Alegre, Rio Grande do Sul. Brazil, 2007 to 2017 (MHD/POA).

Year	Total[a]	Specific by age group					
		15-19	20-29	30-39	40-49	50-59	60 +
2007	5.48	0.00	3.80	7.97	8.44	2.56	0.17
2008	5.34	0.00	4.68	8.62	6.69	2.85	0.17
2009	5.92	0.35	4.24	9.92	6.21	4.27	0.23
2010	6.06	0.53	3.80	10.41	6.53	3.56	0.36
2011	5.55	0.18	4.82	8.46	5.09	3.28	0.42
2012	5.44	0.18	3.22	8.62	7.32	3.99	0.19
2013	4.73	0.53	1.90	6.18	6.69	3.85	0.27
2014	4.14	0.35	0.88	4.39	6.21	4.84	0.27
2015	3.80	0.18	1.32	4.23	5.89	2.99	0.31
2016	3.90	0.00	1.61	3.58	5.73	2.99	0.50
2017	4.52	0.35	1.46	5.04	7.32	3.13	0.42

[a] *Direct standardization, Brazilian population CENSUS 2010 per 100,000 women.*

Regarding stratification by age group, the trend analysis in WLWHIV mortality coefficients indicated a decline in the age groups between 20 and 29 (95%CI -0.566; -0.120). Deaths from HIV/AIDS in women aged 30 to 39 also showed a decrease, however, this was just enough to indicate a stable trend. It is noteworthy that the trend of mortality from HIV/AIDS in women aged 60 and older was increasing (Table 3).

The trend analysis of HIV/AIDS mortality rates in women in Porto Alegre, RS, pointed to differences in skin color during the period. For white and black/brown women, the trend of coefficients was decreasing, whereas for self-declared yellow women it remained stable between 2007 and 2017 (Table 3).

Despite a slight increase in the rates of deaths from HIV/AIDS among women with no education or with incomplete elementary school and a decrease among those with complete elementary school and incomplete high school, both trends did not reach statistical significance. Only the death rates in WLHIV who had incomplete elementary school or higher education showed a decreasing trend and were specifically decreasing (Table 3).

In relation to skin color, HIV/AIDS mortality rates were higher among white women throughout the period investigated. Higher coefficients were also observed among educated women, especially among those with complete elementary school and incomplete high school and those with complete high school and incomplete higher education (Figure 1).

Table 3. Trend in death rates from HIV/AIDS in women living with HIV by sociodemographic characteristics in Porto Alegre, Rio Grande do Sul. Brazil, 2007 to 2017 (MHD/POA).

	Coefficient	95%CI		p-value
Age range				
15 to 19 years	0.013	- 0.035	0.062	0.553
20 to 29 years	- 0.343	- 0.566	-0.120	0.007
30 to 39 years	- 0.459	- 0.917	0.002	0.049
40 to 49 years	- 0.083	- 0.250	0.084	0.292
50 to 59 years	- 0.027	- 0.141	0.194	0.728
60 years and older	0.023	0.003	0.044	0.029
Skin color				
White	- 0.702	- 1.06	- 0.338	0.004
Black/Brown	- 0.371	- 0.640	- 0.101	0.013
Yellow	0.006	- 0.002	0.013	0.136
Education				
No education/incomplete elementary school	0.002	- 0.004	0.008	0.561
Complete elementary school/incomplete high school	- 0.028	- 0.021	0.077	0.232
Complete high school/incomplete higher education	- 0.040	- 0.061	- 0.018	0.002
Higher education	- 0.009	- 0.024	0.006	0.211
Total	-0.144	-0.307	0.019	0.077

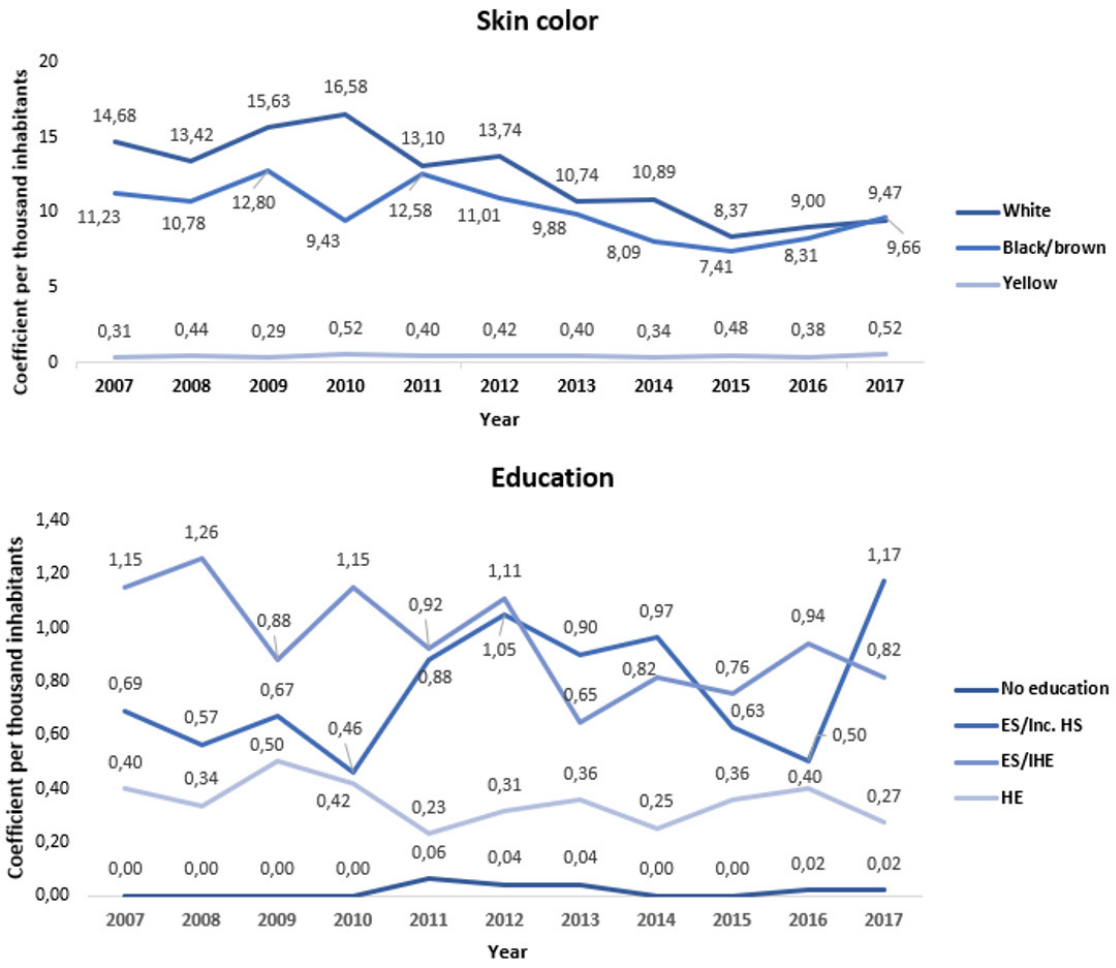

Figure 1. Trend in mortality due to HIV/AIDS, according to skin color and education, in women aged 15 or over, by year of occurrence and age group, in Porto Alegre, Rio Grande do Sul. Brazil, 2007 to 2017 (MHD/POA)

DISCUSSION

ART implementation universally by the Brazilian Health System, from 1996, brought benefits in reducing mortality associated with AIDS.[11] However, the situation in relation to WLWHIV deaths in the city of Porto Alegre reveals persistent inequalities.[5] For the capital of Rio Grande do Sul, our findings revealed the predominance of deaths in young women, with a coefficient above the national one, exceeding the estimates raised in the epidemiological bulletin in 2018,[3] revealing a rate of 4.4/100,000 inhabitants for women aged 30-34 years. Mortality from AIDS in young women follows the high prevalence of the disease in this population, being the main cause of death among those of childbearing age or in pregnant and postpartum women living with HIV/AIDS.[9,12,13] Although the precocity of deaths draws attention and has been identified in previous studies,[4,14] our findings point to a tendency for mortality rates to decline in WLWHIV at childbearing age, especially between 20 and 39 years old, which may be due, in part, to the strategies and initiatives implemented by Porto Alegre's health services from 2010 onwards.[15]

The municipality's management reports between 2010 and 2014 describe that the implementation of strategic actions and the expansion and qualification of health services resulted in a 17% reduction in overall mortality rates due to HIV/AIDS.[15] However, difficulties related to the management of HIV/AIDS care matrix for Primary Health Care (PHC) and healthcare strategies in longitudinal care at this level of care may be related to mortality rates, considering that, in more peripheral areas, where social vulnerabilities are greater, the number of health professionals is smaller compared to central regions, favoring "care gaps".[15,16]

In the same sense, a study on the therapeutic itineraries of cases that resulted in deaths, monitored by the Municipal AIDS Mortality Committee, in the city of Porto Alegre, highlighted weaknesses in access and assistance provided by health services,[10] which may be related to difficulties in identifying and retaining individuals for treating the disease, increasing risk factors. Among the weaknesses identified in assistance, the following stood out: late diagnosis of HIV infection; non-adherence to ART; the loss of opportunity in diagnosis; inadequate

clinical management during hospital stay; failure to carry out diagnostic tests.[10] Failures in access to health services highlighted weaknesses in HIV diagnosis, reception/consultation in specialized services and PHC, among others.[10] Therefore, it is important to expand such analyzes to verify how such inequities are reflected in health care for women, since, even though they use health services more,[17] they continue to have high mortality rates due to HIV/AIDS.

Added to these challenges, stigma associated with diagnosis can generate experiences of social suffering, impacting the possibilities of access to treatment.[18] Furthermore, sociocultural beliefs associated with sex and the prevention of sexually transmitted infections and HIV/AIDS in old age, as well as decreased frequency of gynecological medical care routines and consultations by women in this age group, may justify the late diagnosis and increased mortality in women over 60 years of age identified in our study, following the coefficient found in Ceará.[19] It is considered that older adults with AIDS fall ill and die faster than young people, especially due to difficulties related to taboos that permeate older adults' sexuality and favor late diagnosis of the disease, in addition to the combination of other health problems, such as drug use and exposure to tuberculosis, which accelerate the progression of immunological decline and increase the risk of death.[19] Another relevant issue is that, while women of childbearing age maintain a routine of medical and gynecological monitoring, women in more advanced age groups end up invisible in health systems, since their sexuality is denied and, sometimes, their role as wife does not identify them as potentially vulnerable, which can keep them away from exams and preventive behaviors such as not using condoms.[20] In a study on the sexual behavior of PLWHIV over 50 years of age in Santa Catarina,[21] it was found that 50% of older adults reported not using condoms regularly, regardless of the partner's seropositivity.

Especially, as observed in the present study, women with less education had higher mortality rates, corroborating a national study that indicates higher survival in more educated WLWHIV.[22] Despite not identifying statistically significant trends, it should be noted that low education is associated with worse living conditions, housing, food, transportation, access to health services and social discrimination, which directly impact the population's health.[23]

Higher levels of education can result in greater knowledge about ways to prevent HIV, as well as access to better employment and income conditions, enhancing access to health services and care.[24] Stigma and prejudice can promote barriers, affecting increased mortality in both more vulnerable populations and those with better social conditions. In this regard, sometimes higher levels of education favor access to private health systems and, as they are not considered "key populations" or are identified as having "risky sexual behaviors" or "drug users",[20] access to early diagnosis and treatment of HIV/AIDS are made difficult, reducing the survival rate of PLHIV.[25]

It is noteworthy that white women are the most affected by deaths, following the trend of decreasing mortality rates for this category. For black/brown women, a decrease in coefficients was observed, but smaller in relation to white women, indicating important inequities in the health care scenario.[10] Studies carried out in Brazil, between 2000 and 2007,[25] and in Florida (USA), between 2000 and 2009,[26] point out that black and brown people were the most likely to have recorded mortality related to HIV/AIDS, compared to white individuals. It must be considered that vulnerabilities associated with race/color, especially among black and brown people, increase barriers in access to health services and may favor lower risk perception and lower adherence to ART.[27] Hence, it is possible to think that investments are still necessary to reduce inequities and strengthen care and attention networks for WLWHIV in order to reduce mortality. Especially in Porto Alegre, RS, vulnerabilities related to poverty, race and social class affect women who live in more precarious regions and with a strong presence of violence and drug trafficking.[28]

Even though the economic factor was not assessed in the present study, financial barriers can impact health care and increase mortality levels.[29] Another limitation is underreporting in death records, causing distortions in estimates, but the improvement of records and official statistics has been constant, benefiting the increasing use of this information by health services. Other information on health characteristics and vulnerabilities, as well as socioeconomic specificities and public policies aimed at WLWHIV, can bring new perspectives for research and care in the preventability of deaths.

Investments that favor equal access to education and economic stability and security, especially for women,[30] must be promoted with a view to enhancing their autonomy and reducing health inequities. On the other hand, it is believed that investments in qualification of health care networks' work, such as to encourage continued education through actions that strengthen basic care as an element that organizes care and train teams and community health workers to work with PLWHIV, can also impact mortality indicators among women.

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AUTHORS' CONTRIBUTIONS

Maiton Bernardelli contributed to study conception, planning, data statistical analysis and interpretation and article writing. **Douglas Nunes Stahnke** contributed to study statistical analyzes and critical review and final review. **Tonantzin Ribeiro Gonçalves** guided study planning and contributed to study analysis and critical review and final review. **Marcos Pascoal Pattussi** co-supervised the study and contributed to study analysis and critical review and final review.

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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Severe COVID-19 in the context of a vaccinated population: Case-control study

COVID-19 grave no contexto de uma população vacinada: estudo caso-controle

COVID-19 grave en el contexto de una población vacunada: Estudio de casos y controles

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Corresponding Author:
Oswaldo Sinoe Medina-Gómez
oswaldo.medina@imss.gob.mx

Address: Calle Gabriel Mancera 222, Colonia del Valle Norte, Benito Juárez, Código Postal 03103, Ciudad de México. Unidad de Investigación en Epidemiología Clínica del Hospital General Regional #1 "Dr. Carlos Mac Gregor Sánchez Navarro" del Instituto Mexicano del Seguro Social.

Irving Díaz-Muñoz[1];
Oswaldo Sinoe Medina-Gómez[1];
Gonzalo Ivan Julian-Bello[2];

[1] *Mexican Social Security Institute, IMSS. Hospital General Regional 1 "Dr. Carlos Mac Gregor Sánchez Navarro", Mexico City, CDMX, Mexico.*
[2] *Mexican Institute of Social Security, IMSS. Family Medicine Unit #15, Mexico City, CDMX, Mexico.*

ABSTRACT

Background and Objectives: Since its appearance in 2019, multiple risk factors have been identified for presenting a severe form of COVID-19 and different vaccines have also been developed to prevent severe manifestations. However, despite a vaccination history, some cases progress to complications or even death. The objective of this study was to determine the strength of the association between the severity of COVID-19 and the history of vaccination in patients treated at a public reference hospital in Mexico City. **Methods:** This was a non-experimental, retrospective, and analytical epidemiological study of cases and controls. The study population was people treated at a concentration hospital for COVID-19 care between July 1, 2021, and June 30, 2022, in Mexico City. **Results:** 132 participants (44 cases and 88 controls) were included in the study. The risk factors most strongly associated with COVID-19 severity were age greater than or equal to 60 years, presenting 22 breaths per minute at the first medical evaluation, systolic blood pressure greater than or equal to 140 millimeters of mercury, and a history of at least one chronic comorbidity. However, vaccination history was associated with 94% (OR 0.06) lower odds of developing severe COVID-19 compared to those without a history of vaccination, regardless of the presence of associated risk factors. **Conclusion:** Lacking a history of vaccination and presenting any of the identified risk factors confer higher odds of developing severe forms of the disease.

Keywords: *COVID-19 vaccines. Mass vaccination. Patient acuity. Public Health.*

RESUMO

Justificativa e Objetivos: Desde o seu aparecimento em 2019, foram identificados múltiplos fatores de risco

para a apresentação de uma forma grave de COVID-19 e foram desenvolvidas diferentes vacinas para prevenir o aparecimento de manifestações graves. No entanto, apesar de um histórico de vacinação, alguns casos podem evoluir para complicações ou mesmo para a morte. O objetivo deste estudo foi determinar a força de associação entre a gravidade da COVID-19 e o histórico de vacinação em pacientes atendidos em um hospital público de referência na Cidade do México. Métodos: Estudo epidemiológico não-experimental, retrospectivo e analítico, de casos e controles. A população do estudo foram indivíduos atendidos em um hospital de concentração para atendimento à COVID-19 entre 1 de julho de 2021 e 30 de junho de 2022, na Cidade do México**. Resultados:** 132 participantes (44 casos e 88 controles) foram incluídos no estudo. Os fatores de risco mais fortemente associados à gravidade da COVID-19 foram idade superior ou igual a 60 anos, apresentar 22 respirações por minuto na primeira avaliação médica, pressão arterial sistólica superior ou igual a 140 milímetros de mercúrio e histórico de pelo menos uma comorbidade crônica. No entanto, histórico de vacinação foi associado a uma probabilidade 94% (OR 0,06) menor de desenvolver COVID-19 grave em comparação com aqueles sem histórico de vacinação, independentemente da presença de fatores de risco associados. **Conclusão:** A ausência de histórico de vacinação e a presença de algum dos fatores de risco identificados conferem maiores probabilidades de desenvolver formas graves da doença.

Descritores: *Vacinas contra COVID-19. Vacinação em massa. Gravidade do paciente. Saúde Pública.*

RESUMEN

Justificación y Objetivos: Desde su aparición en 2019, se han identificado múltiples factores de riesgo para presentar una forma grave de COVID-19 y también se han desarrollado distintas vacunas que previenen la aparición de manifestaciones de gravedad. Sin embargo, a pesar del antecedente de vacunación, algunos casos se complican o incluso fallecen**.** El objetivo del este estudio fue determinar la fuerza de asociación entre la gravedad de la COVID-19 con el antecedente de vacunación en pacientes atendidos en un hospital público de referencia de la Ciudad de México. **Métodos:** Estudio epidemiológico no experimental, retrospectivo y analítico, de casos y controles**.** La población de estudio fueron personas atendidas en un hospital de concentración para la atención de COVID-19 entre el 1 de julio de 2021 y el 30 de junio de 2022 en la Ciudad de México. **Resultados:** 132 participantes (44 casos y 88 controles) fueron incluidos en el estudio. Los factores de riesgo más fuertemente asociados con la gravedad de la COVID-19 fueron la edad mayor o igual a 60 años, presentar 22 respiraciones por minuto en la primera valoración médica, tensión arterial sistólica mayor o igual a 140 milímetros de mercurio y el antecedente de al menos una comorbilidad crónica. No obstante, el antecedente de vacunación se asoció con 94% (RM 0.06) menos posibilidades de desarrollar COVID-19 grave con respecto a aquellos sin antecedente vacunal, independientemente de la presencia de los factores de riesgo asociados. **Conclusión:** carecer del antecedente de vacunación y presentar alguno de los factores de riesgo identificados confieren las mayores posibilidades de presentar formas graves de la enfermedad.

Palabras Clave: *Vacunas contra la COVID-19. Vacunación masiva. Gravedad del paciente. Salud Pública.*

INTRODUCTION

Coronaviruses (CoV) are a group of multiple viruses that commonly infect animals and humans, and can cause manifestations with a wide range of severity, from asymptomatic to fatal.[1] In late 2019, the first cases of infection with SARS-CoV-2, the etiologic agent of the respiratory disease that was later named COVID-19, appeared.[2,3]

The World Health Organization (WHO) has established a definition of a severe case of COVID-19: "Adolescent or adult with clinical signs of pneumonia (fever, cough, dyspnea, rapid breathing) plus one of the following: Respiratory rate (RR) >30 breaths/min; severe respiratory distress; or SpO_2 <90% on room air; or acute respiratory distress syndrome (ARDS), sepsis, septic shock, or death".[4]

Risk factors for the development of severe COVID-19 can be studied in at least 5 different groups: Demographic factors (age and sex), symptoms (clinical manifestations), comorbidities, complications, and laboratory indicators.[5]

In response to the high number of severe cases of the disease, vaccines were developed to reduce the occurrence of severe cases of COVID-19. Mexico initiated its national vaccination strategy on December 24, 2020.[6] The prioritization for the use of vaccines followed the recommendations of the Vaccine Technical Advisory Group (GTAV), which included 4 guiding principles: Age of individuals (over 60 years of age), comorbidities, priority groups (including health personnel), and the behavior of the epidemic.[7]

The vaccines used in Mexico during the study period were those developed by Pfizer-BioNTech (BNT162b2 mRNA), Moderna (mRNA-1273), AstraZeneca (ChAdOx1 nCoV-19), Centro NITsEM N. F. Gamaleya (rAd26-rAd25), CanSino (Ad5-nCoV), Sinovac (PiCoVacc) and Janssen (Ad.26.COV2.S).[8] The vaccination strategy avoided commercialization in order to provide equity in access to immunizations in an environment of limited availability whose access to the type of vaccines was within the framework of the COVAX initiative.[9] Mexico City reached a vaccination coverage of 95% of its adult population on

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December 30, 2021.[10] However, between July 1, 2021, and June 30, 2022, 11,858 deaths due to COVID-19 occurred in the country's capital.[11,12] This suggests that deaths continue to occur despite vaccination coverage rates approaching 100%, and it should be emphasized that death is not the only indicator of severity in COVID-19. The aim of this study was to determine the strength of the association between the severity of COVID-19 and the history of vaccination in patients assisted at a public reference hospital in Mexico City.

METHODS

A non-experimental, epidemiological, retrospective, analytical, and case-control study was conducted to determine the strength of the association between a history of vaccination against COVID-19 and the severity of COVID-19. In addition, sociodemographic, clinical, and biochemical covariates that have been associated with COVID-19 severity were analyzed to establish estimates of magnitude and significance regarding how they may influence the disease.

STUDY POPULATION

People treated at the General Regional Hospital #1 "Dr. Carlos Mac Gregor Sánchez Navarro" (HGR 1), during the period from July 1, 2021, to June 30, 2022. Data were collected from clinical, physical, and electronic records. Inclusion criteria were people aged ≥18 years, of any sex, who requested a medical evaluation at HGR1 during the aforementioned period and had valid medical insurance at the Mexican Social Security Institute (IMSS), with polymerase chain reaction (PCR) test or positive rapid antigenic test (RAP) for SARS-CoV-2. Exclusion criteria were evidence of receiving the vaccine against COVID-19 in a country other than Mexico and participants with habitual residence outside Mexico City. The elimination criterion was documented evidence of having had SARS-CoV-2 infection at a time prior to requesting medical care.

Case Definition: A person who meets the screening criteria and who, at the time of seeking care, presented severe COVID-19 criteria suggested by WHO.[4] Control Definition: A person who meets the screening criteria and who, at the time of seeking care, did not present severe COVID-19 criteria suggested by WHO.[4]

The sample size for case-control studies was calculated with the aid of the Epi Info 7.2.5.0 program, considering a safety of 95% and a statistical power of 80%, as well as a ratio of 2 controls for each case. The final sample consisted of 132 participants, 44 cases and 88 controls. The type of sampling was simple random probability. The data source was secondary (clinical record).

The variables of interest were collected in a database. Descriptive analysis was performed to report frequencies, proportions, and percentages for qualitative variables; and measures of central tendency and dispersion for quantitative variables. Chi^2 and Fisher's exact tests were performed to establish whether there were significant differences in proportions between cases and controls. Bivariate analysis employed Student's t-test for independent samples or the Mann-Whitney U test to determine differences between means or between medians, respectively, and in congruence with the distributional nature of the data. Crude odds ratios (OR) were estimated with their respective 95% confidence intervals (CI) and finally, multivariate analysis was performed using multiple logistic regression. The analyses corresponding to the normality, univariate, and bivariate tests were performed with the IBM SPSS version 23 program. The multivariate analysis was performed with the STATA program (College Station, TX, USA) version 14.0. In all cases, a p-value <0.05 was considered statistically significant.

This study used secondary source data and was approved by the local ethics and research committee, under registration number R-2023-3609-002.

RESULTS

Table 1 shows the qualitative characteristics of the 132 participants in this study, grouped according to whether they belonged to the case or control group. The history of vaccination was considered present if the record explicitly mentioned it, even if it was not possible to identify the brand or specific name of the vaccine. Only 34.1% of the cases had evidence of having been vaccinated, while this history was found in 81.8% of the controls ($p < 0.001$). All cases were complete schedules, whose second dose was administered at least 14 days before the onset of COVID-19 symptoms.

The differences between sexes were not significant ($p = 1.000$) because the design and selection of participants ensured that the proportion of men and women were equal between cases and controls, considering that there were 2 controls for each case.

Most of the symptoms and comorbidities related to the severity of COVID-19 had statistically significant differences depending on the study group ($p<0.05$). Among complications (coagulopathy or acute kidney injury), there were no statistically significant differences.

Table 2 shows the quantitative characteristics of the 132 participants in this study. Cases had a median age of 71 years old with an interquartile range (IQR) of 63.00 - 79.50; whereas controls had a significantly lower median age (41 years, IQR 25 - 58.5; $p <0.001$).

No statistically significant differences were found between the median BMI of the cases (25.64 kg/m2) and that of the controls (25.33 kg/m2; $p = 0.572$). Systolic blood pressure (SBP) recorded during the first medical evaluation showed significant differences (129.77 ± 13.10 mmHg) between cases and controls (115.93 ± 16.62 mmHg), $p < 0.001$; as did diastolic blood pressure (DBP) in cases (95, IQR 90 - 100 mmHg) compared to controls (89, RIC 71 - 97 mmHg); $p = 0.003$.

In the white formula, significant differences were only found in lymphocytes and eosinophils (both absolute and relative), as well as in the percentage of basophils.

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Table 1. Characteristics of participants according to whether they belonged to the case or control group (qualitative variables), HGR1, IMSS, Mexico City, Mexico 2021 - 2022.

Variable (n†)		Case (n= 44) n (%)	Control (n= 88) n (%)	p-value
Vaccination history (132)				
	Yes	15 (34.1)	72 (81.8)	<0.001
	No	29 (65.9)	16 (18.2)	
Sex (132)				
	Male	25 (56.8)	50 (56.8)	1.000
	Female	19 (43.2)	38 (43.2)	
Form of diagnosis (132)				
	PCR	34 (77.3)	28 (31.8)	<0.001
	PAR	10 (22.7)	60 (68.2)	
Type of patient (132)				
	Outpatient	2 (4.5)	61 (69.3)	<0.001
	Inpatient	42 (95.5)	27 (30.7)	
Fever (132)				
	Present	31 (70.5)	36 (40.9)	0.002*
	Absent	13 (29.5)	52 (59.1)	
Dyspnea (132)				
	Present	40 (90.9)	22 (25.0)	<0.001*
	Absent	4 (9.1)	66 (75.0)	
Gastrointestinal symptoms (132)				
	Present	0 (0)	9 (10.2)	0.029*
	Absent	44 (100)	79 (89.8)	
Comorbidities (132)				
	At least one	41 (93.2)	43 (48.9)	<0.001*
	None	3 (6.8)	45 (51.1)	
Arterial Hypertension (132)				
	Present	22 (50.0)	21 (23.9)	0.003*
	Absent	22 (50.0)	67 (76.1)	
Diabetes Mellitus (132)				
	Present	14 (31.8)	9 (10.2)	0.003*
	Absent	30 (68.2)	79 (89.8)	
COPD (132)				
	Present	5 (11.4)	1 (1.1)	0.016*
	Absent	39 (88.6)	87 (98.9)	
CKD (132)				
	Present	9 (20.5)	1 (1.1)	<0.001*
	Absent	35 (79.5)	87 (98.9)	
Cancer (132)				
	Present	6 (13.6)	1 (1.1)	0.006*
	Absent	38 (86.4)	87 (98.9)	
HIV infection (132)				
	Present	1 (2.3)	3 (3.4)	1.000*
	Absent	43 (97.7)	85 (96.6)	
Smoking (132)				
	Present	3 (6.8)	5 (5.7)	1.000*
	Absent	41 (93.2)	83 (94.3)	
Complications (63)				
	At least one	11 (55.0)	7 (53.8)	1.000*
	None	9 (45.9)	6 (46.2)	
AKI (58)				
	Present	5 (13.9)	7 (31.8)	0.180*
	Absent	31 (86.1)	15 (68.2)	
Coagulopathy (27)				
	Present	6 (33.6)	0 (0.0)	0.071
	Absent	12 (66.7)	9 (100)	

†Values may vary because the variable was not measured in all participants.
**Fisher's exact test; COPD: Chronic Obstructive Pulmonary Disease; CKD: Chronic Kidney Disease; AKI: Acute Kidney Injury.*

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Table 2. Characteristics of participants according to whether they belonged to the case or control group (quantitative variables), HGR1, IMSS, Mexico City, Mexico 2021 - 2022.

Variable (measurement unit)	Case (n= 44)			Control (n= 88)			
	n†	Median	IQR	n†	Median	IQR	p-value
Age (years)	44	71	63.00 – 79.50	88	41	25.00 – 58.50	<0.001
Body mass index (Kg/m^2)	43	25.64	23.29 – 28.34	84	25.33	22.89 – 27.65	0.572
Body temperature (°C)	44	37.00	36.30 – 38.05	85	36.80	36.3 – 37.8	0.352
Respiratory rate (rpm)	44	20	18 - 24	85	19	18 - 20	<0.001
Oxygen saturation (%)	44	90	88 -92	84	94	91 - 96	<0.001
Diastolic blood pressure (mmHg)	44	95	90 - 100	85	89	71 - 97	0.003
Leukocytes (celx10^3 /µl)	42	9.40	6.61 – 14.50	26	8.85	5.28 – 12.10	0.235
Absolute neutrophils (celx10^3 /µl)	42	6.81	4.58 – 12.94	26	6.25	3.26 – 10.51	0.223
Percentage of neutrophils (%)	42	84.00	78.00 – 88.70	26	79.20	61.40 – 87.10	0.067
Absolute lymphocytes (celx10^3 /µl)	42	0.68	0.48 – 1.05	26	1.23	0.79 – 2.01	0.004
Percentage of lymphocytes (%)	42	7.20	4.20 – 13.00	26	14.90	5.60 – 28.00	0.014
Neutrophil/Lymphocyte Ratio	42	10.90	6.29 – 22.30	26	5.40	2.09 – 15.13	0.019
Absolute eosinophils (celx10^3 /µl)	42	0.01	0.00 – 0.09	26	0.045	0.01 – 0.12	0.047
Percentage of eosinophils (%)	42	0.10	0.00 – 0.60	26	0.50	0.10 – 1.20	0.024
Absolute basophils (celx10^3 /µl)	42	0.03	0.01 – 0.05	26	0.04	0.02 – 0.05	0.261
Percentage of basophils (%)	42	0.30	0.20 – 0.40	26	0.40	0.30- 0.50	0.037
Urea nitrogen (mg/dl)	21	27.90	17.70 – 61.50	14	20.95	16.40 – 24.00	0.249
Creatinine (mg/dl)	42	1.15	0.7 – 2.44	26	1.04	0.92 – 1.42	0.980
Glucose (mg/dl)	42	129.50	91.00 – 177.00	26	119.96	86.00 – 139.00	0.057
Prothrombin time (s)	18	16.10	15.00 – 17.60	14	14.65	13.00 – 15.90	0.041
	n	**Average**	**SD**	**n**	**Average**	**SD**	**p-value**
Systolic blood pressure (mmHg)	44	129.77	13.10	85	115.93	16.62	<0.001
Activated partial thromboplastin time (s)	18	32.05	4.45	14	30.47	3.79	0.288
Platelets (plat/l)	42	244.56	145.15	26	248.50	100.59	0.986

†Values may vary because the variable was not measured in all participants.
IQR: Interquartile range; SD: Standard deviation; m: meters; Kg: Kilograms; °C: degrees Celsius; rpm: respirations per minute; mmHg: millimeters of mercury; µl: microliter; ml: milliliter; l: liter; mg: milligrams; dl: deciliter; s: seconds.

There was also a significant difference between the medians of the neutrophil/lymphocyte index (NLI) which was 10.90 (IQR 6.29 - 22.30) for the cases and 5.40 (IQR 2.09 - 15.13) for the controls, p = 0.019. The rest of the determinations of the white formula and the platelet count were not statistically significant.

Table 3 shows the crude ORs for the different variables that were significant in Tables 1 and 2. It can be seen that, in this study, a history of vaccination is associated with 89% (95% CI 71.8 - 95.4) less chance of belonging to the group of cases (calculated as 1 - OR x 100) and, therefore, of having presented more severe manifestations of COVID-19.

Age older than 60 years was associated with an almost 17-fold increased probability of belonging to the case group (OR 16.86, 95% CI 6.55 - 43.38). A history of fever (OR of 3.44, 95% CI 1.59 - 7.47), respiratory rate (RR) ≥22 breaths per minute (rpm) (OR 34.58, 95% CI 7.54 - 158.57), an SBP ≥140 mmHg (OR 9.45 95% CI 2.88 - 30.99) and a DBP ≥90 mmHg (OR 3.07 95% CI 1.38 - 6.86) measured at the first medical assessment, were also associated with a greater chance of belonging to the case group.

The presence of at least one comorbidity increased the odds of having a severe case of COVID-19 with an OR of 14.30 (95% CI 4.12 - 49.65), as did lymphopenia (OR 4.72, 95% CI 1.65 - 13.49), eosinopenia (OR 3.00, 95% CI 1.07 - 8.43) and neutrophil/lymphocyte ≥3 (OR 3.92, 95% CI 1.14 - 13.97).

Table 4 presents the multiple logistic regression model with the highest explanatory power (pseudo r2 = 0.57, n = 129) for the variables associated with severe forms of COVID-19. This model shows that a history of vaccination still reduces the chances of presenting severe COVID-19 by 94% (OR 0.06, 95% CI 0.01 - 0.28), even when adjusting for age groups, RR, SBP, and presence of comorbidity.

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Table 3. Crude odds ratio for vaccination history and variables associated with the presentation of severe COVID-19, HGR1, IMSS, Mexico City, Mexico 2022.

Variable (n†)		Case (n= 44) n (%)	Control (n= 88) n (%)	OR	CI 95%
Vaccination history (132)					
	Absent	29 (65.9)	16 (18.2)	1.00	0.04 – 0.28
	Present	15 (34.1)	72 (81.8)	0.11	
Age group (132)					
	<60 years	7 (15.9)	67 (76.1)	1.00	6.55 – 43.38
	≥60 years	37 (84.1)	21 (23.9)	16.86	
Fever (132)					
	Absent	31 (70.5)	36 (40.9)	1.00	1.59 – 7.47
	Present	13 (29.5)	52 (59.1)	3.44	
Respiratory rate (129)					
	<22 rpm	20 (45.5)	2 (2.4)	1.00	7.54 – 158.57
	≥22 rpm	24 (54.5)	83 (97.6)	34.58	
Systolic blood pressure (129)					
	<140 mmHg	14 (31.8)	4 (4.7)	1.00	2.88 – 30.99
	≥140 mmHg	30 (68.2)	81 (95.3)	9.45	
Diastolic blood pressure (129)					
	<90 mmHg	33 (75.0)	42 (49.4)	1.00	1.38 – 6.86
	≥90 mmHg	11 (25.0)	43 (50.6)	3.07	
Comorbidities (132)					
	None	3 (6.8)	45 (51.1)	1.00	4.12 – 49.65
	At least one	41 (93.2)	43 (48.9)	14.30	
Arterial hypertension (132)					
	Absent	22 (50.0)	67 (76.1)	1.00	1.48 – 6.88
	Present	22 (50.0)	21 (23.9)	3.19	
***Diabetes Mellitus* (132)**					
	Absent	30 (68.2)	79 (89.8)	1.00	1.61 – 10.46
	Present	14 (31.8)	9 (10.2)	4.10	
COPD (132)					
	Absent	39 (88.6)	87 (98.9)	1.00	1.26 – 98.67
	Present	5 (11.4)	1 (1.1)	11.15	
CKD (132)					
	Absent	35 (79.5)	87 (98.9)	1.00	2.73 – 183.22
	Present	9 (20.5)	1 (1.1)	22.37	
Cancer (132)					
	Absent	38 (86.4)	87 (98.9)	1.00	1.60 – 118.05
	Present	6 (13.6)	1 (1.1)	13.74	
Lymphocytes (68)					
	≥1 celx10^3 /µl	12 (28.6)	17 (65.4)	1.00	1.65 – 13.49
	<1 celx10^3 /µl	30 (71.4)	9 (34.6)	4.72	
Neutrophil/lymphocyte ratio (68)					
	<3	5 (11.9)	9 (34.6)	1.00	1.14 – 13.47
	≥3	37 (88.1)	17 (65.4)	3.92	
Eosinophils (68)					
	≥0.02 celx10^3 /µl	18 (42.9)	18 (69.2)	1.00	1.07 – 8.43
	<0.02 celx10^3 /µl	24 (57.1)	8 (30.8)	3.00	

†Values may vary because the variable was not measured in all participants.
OR: Odds ratio; CI 95%: Confidence interval at 95%; COPD: Chronic Obstructive Pulmonary Disease; CKD: Chronic Kidney Disease; rpm: respirations per minute; mmHg: millimeters of mercury.

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Table 4. Adjusted odds ratio for vaccination history and variables associated with the presentation of severe COVID-19, HGR1, IMSS, Mexico City, Mexico 2022.

Variable	SEVERE COVID-19		
	OR	CI 95%	p-value
Without vaccination history	1.00	0.01 – 0.28	<0.001
With vaccination history	0.06		
Age <60 years	1.00	3.30 – 75.99	0.001
Age ≥60 years	15.85		
Respiratory rate <22 rpm	1.00	1.79 – 51.36	0.008
Respiratory rate ≥22 rpm	9.59		
Systolic blood pressure <140 mmHg	1.00	1.01 – 33.27	0.049
Systolic blood pressure ≥140 mmHg	5.78		
No comorbidity	1.00	1.06 – 41.98	0.043
At least one comorbidity	6.68		

n= 129; Pseudo r2 = 0.57
CI 95%: Confidence interval at 95%; rpm: respirations per minute; mmHg: millimeters of mercury

DISCUSSION

In this study, vaccination history was associated with up to 94% lower odds of developing severe COVID-19 compared to those without vaccination history, regardless of the presence of the risk factors most strongly associated with severe manifestations, highlighting the importance of vaccination against COVID-19 and the need to prioritize older adults to benefit from this strategy.

These findings are consistent with results obtained in various settings, for example, an investigation in the United States measured the joint efficacy for the prevention of severe forms of COVID-19 of two different vaccines (BNT162b2 mRNA and mRNA-1273), reporting a decrease of 86.9% (95% CI 80.4 - 91.2).[13] Similar results were reported by other researchers in the United Kingdom, who determined that prior vaccination with BNT162b2 mRNA and ChAdOx1 nCoV-19 mRNA was associated with lower odds of being hospitalized among persons older than 80 years (71.4% and 80.4%, respectively).[14]

Similarly, a case-control study conducted in Israel reported that vaccination with two doses of BNT162b2 mRNA, with the second dose being given at least 7 days before a SARS-CoV-2 infection, was able to prevent hospitalization in 87% (95% CI 55-100) and severe disease in 92% (95% CI 75-100).[15]

Regarding lower-income countries, in India, receiving two doses of ChAdOx1 nCoV-19 vaccine, the last dose being at least 14 days before the onset of symptoms of SARS-CoV-2 infection, was found to be associated with 81.5% (95% CI 79.9 - 99) lower odds of moderate to severe disease.[16] Meanwhile, in Argentina, a case-control study that measured the effectiveness of three different vaccines (rAd26-rAd25, ChAdOx1 nCoV-19, and BBIBP-CorV) in preventing deaths from COVID-19 in people over 60 years of age reported that these vaccines were associated with 93.1% (95% CI 92.6 - 93.5), 93.7% (95% CI 93.2 - 94.3), and 85.0% (95% CI 84.0 - 86.0) lower chances of death.[17]

It has been published that age over 60 years is a risk factor for severe COVID-19.[1,5,18] In this study, age was statistically different between cases and controls (this study is not age-matched), which is consistent with the reported findings.

Respiratory rate greater than 30 breaths per minute (rpm) is part of the operational case definition[4] and therefore, considering this cutoff point would result in significant associations due to collinearity. However, if the cutoff point is reduced to 22 rpm, a parameter considered in the q-SOFA scale,[19] it is possible to determine whether less marked RR elevations may be associated with the presence of COVID-19 severity. In this work, RR ≥22 rpm was associated with greater chances of belonging to the group of cases.

While systemic arterial hypertension has been linked to COVID-19 severity,[20-22] the findings presented in this study suggest that systolic blood pressure figures at first medical assessment ≥140 mmHg are associated with increased risk of severity regardless of history of arterial hypertension.

Regarding comorbidities, the results presented here are consistent with those reported by a study conducted in China (n = 1,099), which identified that the presence of at least one comorbidity out of 9 possible (including COPD, diabetes, hypertension, cancer, and CKD) was significantly present among those with severe COVID-19 (38.72%, 95% CI 31.43 - 46.41) compared to those with a non-severe case (20.95%, 95% CI 18.37 - 23.71).[23]

The primary limitation of this study is that the main independent variable, i.e., vaccination history, was obtained from the clinical record, since Mexico does not have an open database that allows health professionals to access confirmation of such history through official records endorsed by the health authority. It should be noted that this is a retrospective study whose source of information consisted of clinical records (physical and/

or electronic), so the variables were not collected for the specific purposes of this research, which implies a decrease in the precision of the measurement and, above all, the availability of some variables, particularly in the group of controls, a significant proportion of whom received outpatient management, which leads to an underreporting of laboratory indicators that could have been useful to improve the quality of the results presented here.

In contrast, the selection criteria and the randomization of the sample made it possible to avoid systematic biases, mainly selection bias, and at the same time, the sample obtained was representative of the source population and exposure. Among the strengths, this study made it possible to establish the magnitude and meaning of the associations found between the severity of COVID-19 and different covariates that, despite having already been recognized as risk factors for presenting manifestations of severity, to the knowledge of the researchers involved in this study, this is the first time that they have been explored in the context of mass vaccination, This is relevant because it has been carried out in a developing country, demonstrating the importance of the vaccination strategy and adding evidence to raise public awareness of the need to have a complete vaccination schedule against COVID-19 and to set a precedent for future cases of other emerging or reemerging diseases that could present scenarios similar to the one recently presented.

It has been documented that the population of several Latin American countries faced fear and distrust of receiving hastily developed vaccines due to the state of emergency, nuanced by diverse political and social contexts.[24] However, studies such as this one highlight the benefits of mass vaccination and support the intersectoral efforts made by international agencies, governments, the scientific community, and the private sector to promote health protection through the development, implementation, and equitable accessibility of immunizations.

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AUTHORS' CONTRIBUTIONS

Irving Díaz-Muñoz contributed with the bibliographic research, abstract writing, introduction, methodology, discussion, interpretation and description of results, preparation of tables, conclusions, revision, and statistics. **Oswaldo Sinoe Medina-Gómez** contributed to the project management, abstract writing, methodology, discussion, interpretation and description of results and conclusions, and review of statistics. **Gonzalo Ivan Julian-Bello** contributed to the project management, methodology, interpretation of results, statistics, conclusions, and revision of the final manuscript.

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

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ORIGINAL ARTICLE

Socio-environmental factors contributing to the high incidence of COVID-19 in a border city in northern Uruguay

Fatores socioambientais que contribuem para alta incidência de COVID-19 em cidade fronteiriça no norte do Uruguai

Factores socioambientales que contribuyen a alta incidencia de COVID-19 en ciudad fronteriza del norte de Uruguay

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Corresponding Author:
Mariana Gomez-Camponovo
mgomez@cup.edu.uy

Address: Florida 1065, Paysandú, Uruguay.

Marcel Achkar[2];
Mariana Gomez-Camponovo[1];
Nicolas Perez[2];
Eleuterio Umpierrez[2];

[1] *Universidad de la República. Paysandú, Uruguay.*
[2] *Universidad de la República. Montevideo, Uruguay.*

ABSTRACT

Background and Objectives: the present study was conducted in the city of Rivera, situated in northern Uruguay on the border with Brazil. The disease initially progressed slowly in 2020, with subsequent outbreaks followed by a rapid increase in incidence. The objective was to explore the relationship between the spatial distribution of COVID-19 cases in a binational city and variables such as socioeconomic status, population density, and mobility patterns, with the aim of informing public policies. **Methods**: an exploratory study was conducted between August 2020 and January 2021 using data obtained from the Ministry of Health. The explanatory variables considered included population density, socioeconomic level, and mobility. Three distinct periods from 2020 to 2021 were identified. Spatial autocorrelation was analyzed using Moran's Index and the Gi* statistic (Getis & Ord). Hierarchical cluster analysis was employed to identify homogeneous groups of census segments. **Results**: a total of 1,846 cases were georeferenced. Through hierarchical cluster analysis, seven homogeneous groups were identified. Mobility was found to explain the incidence of cases among the high socioeconomic level group, while population density accounted for the differences observed in the low socioeconomic group. **Conclusion**: in this city, priority should be given to populations residing in areas with higher population density and greater mobility. This small-scale territorial analysis provides valuable information for developing localized policies aimed at addressing health crises.

Keywords: *COVID-19. Spatial-temporal Analysis. Social Mobility. Socioeconomic Level. Population Density.*

RESUMO

Justificativa e Objetivos: o presente estudo foi realizado na cidade de Rivera, localizada no norte do Uruguai, na fronteira com o Brasil. A doença progrediu lentamente durante 2020, com surtos subsequentes seguidos por um

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rápido aumento na incidência. O objetivo foi explorar a relação entre a distribuição espacial dos casos de COVID-19 em uma cidade binacional e variáveis como nível socioeconômico, densidade populacional e padrões de mobilidade, com o objetivo de informar políticas públicas. **Métodos**: estudo exploratório foi realizado entre agosto de 2020 e janeiro de 2021 com dados do Ministério da Saúde. As variáveis explicativas incluíram densidade populacional, nível socioeconômico e mobilidade. Três períodos distintos de 2020 a 2021 foram identificados. Autocorrelação espacial foi analisada com o Índice de Moran e a estatística Gi* (Getis & Ord). Utilizando a análise de *cluster* hierárquico, foi possível identificar grupos homogêneos de segmentos censitários. **Resultados:** um total de 1.846 casos foi georreferenciado. Através da análise de *cluster* hierárquico, sete grupos homogêneos foram identificados. A mobilidade foi encontrada como explicativa para a incidência de casos no grupo de alto nível socioeconômico, enquanto a densidade populacional explicou as diferenças observadas no grupo de baixo nível socioeconômico. **Conclusão**: nessa cidade, as populações a serem priorizadas são aquelas que residem em áreas com maior densidade populacional e maior mobilidade. Essa análise territorial em pequena escala fornece informações valiosas para o desenvolvimento de políticas locais destinadas a lidar com crises de saúde.

Descritores: *COVID-19. Análise Espaço-temporal. Mobilidade Social. Nível Socioeconômico. Densidade Demográfica..*

RESUMEN

Justificación y Objetivos: el estudio se realizó en la ciudad de Rivera, situada en el norte del país en la frontera con Brasil. La enfermedad progresó lentamente durante 2020, con brotes posteriores seguidos de un rápido aumento de la incidencia. El objetivo fue explorar la relación entre la distribución espacial de los casos de COVID-19 en una ciudad binacional y variables como nivel socioeconómico, densidad poblacional y patrones de movilidad, con el objetivo de informar políticas públicas. **Métodos**: se realizó un estudio exploratorio entre agosto 2020 y enero 2021 con datos del Ministerio de Salud, considerando semanas epidemiológicas. Las variables explicativas consideradas fueron densidad poblacional, nivel socioeconómico y movilidad. Se identificaron tres periodos temporales desde agosto 2020 hasta enero 2021. Se analizo la autocorrelación espacial empleando el Índice de Moran y estadística Gi* (Getis & Ord). Mediante el análisis de *cluster* jerárquico, fue posible identificar grupos homogéneos de segmentos censales. **Resultados**: se georreferenciaron un total de 1.846 casos. Mediante análisis de *cluster* jerárquico, se identificaron siete grupos homogéneos. Para el nivel alto socioeconómico, la movilidad es el factor explicativo de una mayor incidencia de casos. Mientras que, para para el grupo de nivel bajo, la densidad de la población fue el factor explicativo de las diferencias en la presentación de la enfermedad. **Conclusión:** la población a ser priorizada en esta ciudad corresponde a aquellas zonas con mayor densidad poblacional y donde se incrementa la movilidad. El análisis territorial a pequeña escala genera información para la construcción de política local, ante una crisis sanitaria, que la hace más eficaz.

Palabras Clave*: COVID-19. Análisis Espacio-temporal. Movilidad Social. Nivel Socioeconómico. Densidad de Población.*

INTRODUCTION

The first COVID-19 cases were detected in Uruguay on March 13, 2020. Multiple measurements indicated a low incidence initially,[1] and any outbreaks that occurred were studied and controlled through non-pharmacological measures. However, a significant increase in the number of cases began in October 2020.

In January 2021, the cumulative incidence and mortality rates in Brazil were 4,118.3 and 101.3 per 100,000 inhabitants, respectively. In Argentina, these rates stood at 4,101.8 and 103.1 per 100,000 inhabitants, while in Paraguay they were 1,771.7 and 36.2 per 100,000, respectively. Uruguay recorded an incidence rate of 1,041.2 and a mortality rate of 10.5 per 100,000 inhabitants.[2] Before the study period (August 2020 to January 2021), the Ministry of Public Health issued its last report on July 28, 2020, which documented 1,218 COVID-19 cases in Uruguay, resulting in an incidence rate of 34.5 per 100,000 inhabitants.[3] As of February 14, 2021, there were 48,909 laboratory-confirmed cases in Uruguay, with a cumulative incidence rate of 1,385.17 cases per 100,000 inhabitants.[4]

Considering the significant increase in cases between August 2020 and January 2021, this time frame was chosen as the study period for this research.

Rivera, located in northern Uruguay, shares a permeable border with the city of Santana do Livramento, Brazil. The border is traversed by a single street, posing challenges for effective control measures. The majority of the population has dual citizenship, and many workers provide services on both sides of the border, including health care workers. This region has garnered consistent attention due to the high volume of people freely moving across the border, which increases the risk of introducing new variants.

The association between SARS-CoV-2 and public transport has been recognized as important;[5-7] however, the Uruguayan and Brazilian sides of the city of Rivera do not share transportation. Nevertheless, Rivera has witnessed a proliferation of tax-free stores known as free

shops, which serve as a significant driver for the local economy, creating employment opportunities and facilitating a continuous flow of people crossing the border. The commercial area is situated in the city center and in close proximity to the street that connects this binational city.

In October 2020, Rivera, a department in Uruguay, recorded the highest cumulative incidence of COVID-19 cases in the entire country, higher than all other departments, including the capital city of Montevideo.[8] Joint actions were taken by health authorities on both sides of the border to diagnose COVID-19, follow up on detected cases, exchange epidemiological information, and adopt measures for travelers, among others.[9] The vaccination program in Uruguay commenced in March 2021, initially targeting specific priority groups. It is important to consider the socioeconomic disparities within the population of Rivera as this can influence the characterization of the epidemiological situation.[10] Population density is another crucial factor to be considered.[11] Higher population density is typically associated with increased incidence and is often linked to more densely populated areas.[12]

Certain models have suggested that maintaining physical distance may not significantly contribute to disease transmission.[13] However, this study considers mobility as an important variable in analyzing disease transmission. It is worth noting that some authors argue that measures restricting mobility have not effectively prevented the progression of the pandemic.[14] Some authors have approached mobility differently by utilizing categories provided by the data provider (https://www.google.com/covid19/mobility/?hl=es). These categories take into account various levels of mobility, such as being in a park or a residential unit, as opposed to being in workplaces, stores, pharmacies, or using public transportation. Conversely, other studies treated all mobility categories equally in their analyses.[15]

It is necessary to understand the structural elements within spaces that can help explain the problem under study.[16] Consequently, the distribution of the subject under study is analyzed by considering demographic, environmental, and socioeconomic variables of the population. Moreover, the behavior of the subject in space is examined to draw meaningful conclusions. The present study examined the pre-existing structural conditions within the city that are likely to account for the fluctuations in the number of COVID-19 cases.

The objective was to explore the relationship between the spatial distribution of COVID-19 cases in a binational city and variables such as socioeconomic status, population density, and mobility patterns, with the aim of informing public policies.

METHODS

The city of Rivera, located at the coordinates 55° 33'3"W; 30° 54'19"S, is part of a conurbation space along with the city of Santana do Livramento Brazil, where 155,221 people reside in a binational city with a dry border. Rivera has a population of 78,900 (ine.gub.uy), 53% of which are women. In total, 11.7% of households fall below the poverty line, 49.6% are not connected to the general sanitation network and 8.9% are not connected to the drinking water distribution network. Those who are 25 years of age and older have an average of 8.1 years of education, the lowest in Uruguay. Labor market indicators show the activity rate (55.2%) and employment rate (50.4%) to be below the national average, and the percentage of informal work is among the highest, with 42% of employed persons not contributing to social security.[17]

The present study was conducted in this city, located in northern Uruguay, focusing on the period when the cases were on the rise. It shares a border with Brazil, which adds complexity to the analysis of the problem to be addressed. This research includes an analysis of the socio-environmental variables that may have contributed to the transmission of the virus.

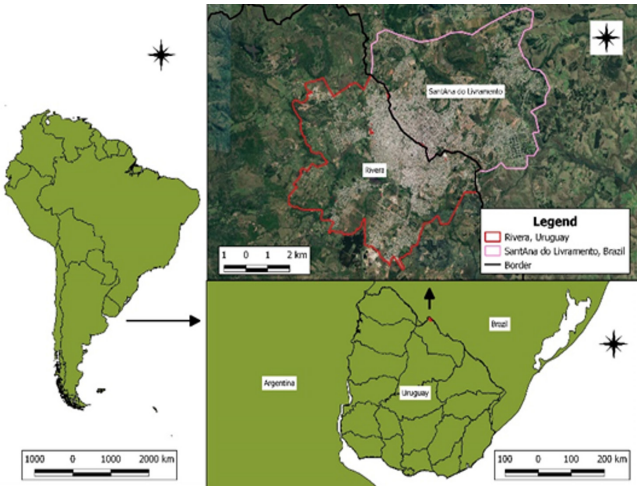

Figure 1. The city of Rivera, Uruguay.

This is an exploratory study. The data of COVID-19 cases were obtained from the Ministry of Health's surveillance system (https://www.gub.uy/ministerio-salud-publica/home), incorporating incident cases within the census segment from August 2020 to January 2021. Throughout this timeframe, a cumulative total of 2,277 COVID-19 cases were reported.

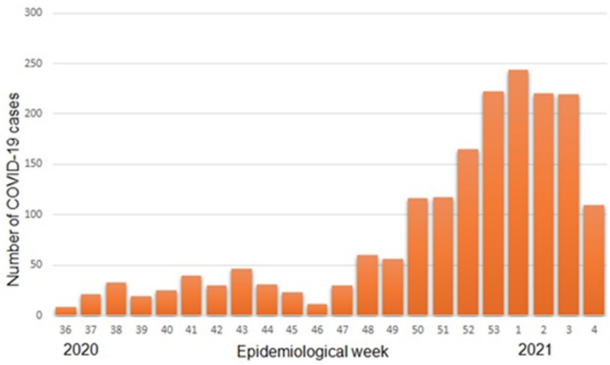

Figure 2. COVID 19 cases in the city of Rivera, Uruguay, according to epidemiological week, 2020-2021.

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By conducting a detailed analysis of the cases that were reported, it was found that some of them were outside the study area, many of which were in the neighboring city of Santana do Livramento, Brazil. After this analysis, 1,846 cases were included, which are presented according to epidemiological week (Figure 2).

In terms of temporality, the data were distributed according to epidemiological weeks (22 in total), and with regard to spatial data, the census segment (administrative unit) was used (59 segments for the city of Rivera). The population density per segment was calculated in real values expressed in inhabitants per square kilometer, based on data from the 2011 census (www.ine.gub.uy). They are sorted according to their standard deviation in relation to mean.

A socioeconomic status indicator was computed for each administrative unit, defined as census segments, using data sourced from the 2011 census conducted by the Uruguayan National Statistics Institute (www.ine.gub.uy). The variables considered encompassed housing conditions, wall material, primary roof material, drinking water supply, persons per bedroom, waste disposal system, energy source for cooking, household internet access, unmet basic needs (three or more), ethnicity, education, basic formal educational level, and social security income.[18]

The construction of this socioeconomic indicator involved employing principal factor analysis,[10] utilizing Stata version 11 for statistical analysis. The first factor explained 73.5% of the variance in the original variables within the model. Following this, the distribution of this factor was divided into quartiles to depict socioeconomic levels.

The formula utilized for computing the socioeconomic indicator is delineated as follows:

$$\gamma_{ij} = \sum_{k=1}^{q} z_{ik} b_{kj} + e_{ij} \qquad \text{(Harman, 1976)}$$

Where
y_{ij} is the *i*th observation of the *j*th variable;
z_{ik} is the *i*th observation of the *k*th of the common factor;
b_{kj} is factor loading;
e_{ij} is a unique factor of the *j*th's variable.

Mobility data were obtained from smartphones and handle devices (https://www.google.com/covid19/mobility/?hl=es) that agreed to provide location data. They were classified by location according to the following categories: retail and recreation; parks; grocery stores and pharmacies; workplaces; transport "transit" hubs; and residential areas.[15] Each value was compared to a baseline value (five weeks, from January 3 to February 6, 2020), and the data used was the percentage change[15] relative to that baseline value. The reference value was the median. In the study for each census segment, mean mobility was weighted according to the number of cases during each epidemiological week.

The temporal behavior of cases presented three periods in 2020 and 2021: period one was stable, from weeks 36 to 46; period two had rapid growth from weeks 47 to one; and period three was stable and declining from weeks two to four (Figure 2).

The number of cases and mobility was grouped according to those three periods, which resulted in eight variables, namely: the number of cases per segment during periods one, two, and three; mobility, weighted by the number of cases in each segment during periods one, two and three; and population density (inhabitants/km^2) and socioeconomic level for each segment. The eight variables that were used throughout the analysis were thereby defined.

The behavior of the pandemic in a medium-sized city was explored based on census segments,[16] which represented administrative divisions that were roughly equal to neighborhoods. By using these segments, it was possible to identify variations in conditions related to positive cases as well as variables that characterized the population. In this regard, local differences within a medium-sized city could be represented. So as not to assume a spatial correlation among the variables, which would be expected from a homogeneous medium-sized city, autocorrelation was assessed using Moran's Index.[19] The Gi*statistic was used to identify the degree of spatial correlation for each variable in each segment. A matrix was built that included the census segments and the distribution of the variables in those segments.

The relationships among the variables were detected using a regression tree hierarchical cluster analysis, with the standardized values of the local Gi* statistic for each variable. It was thereby possible to identify groups of segments in which the values of the variable behaved similarly. These clusters were spatialized in a geographic information system to analyze the spatial patterns of the distribution of COVID-19 cases to contribute to possible explanations for this behavior.

All of the data were geocoded with a geographic information system using ArcGIS© 10.4. To assess the spatial autocorrelation of the variables, Moran's global spatial autocorrelation index (Moran's I) was used as follows:

$$I = \frac{n}{S_0} \frac{\sum_{i=1}^{n} \sum_{j=1}^{n} \omega_{i,j} z_i z_j}{\sum_{i=1}^{n} z_i^2} \qquad \text{(Moran, 1948)}$$

Where
z_i is the deviation of an attribute for feature *i from its mean* $(x_i - \bar{X})$;
$\omega_{i,j}$ is the spatial weight between features *i* and *j*;
S_0 is the aggregate of all the spatial weights.

$$S_0 = \sum_{i=1}^{n} \sum_{j=1}^{n} \omega_{i,j} z_i z_j$$

A positive spatial autocorrelation was identified for each of the eight variables. The general Gi* statistic (Getis & Ord) was then used, with census segments as the

spatial unit. The general Gi* statistic is a global method to quantify the degree of spatial autocorrelation of each variable. It measures how autocorrelation varies locally in the study area and calculates a value for each geographic entity (census segment).

The local mean for an entity and its neighbors is proportionally compared to the mean for the whole set. A matrix of weights is used to calculate the local mean, which is a function of the distance (*d*) between the point considered and its neighbors. This matrix, $\omega_{ij}(d)$, takes values of 0 for distant points and 1 for points with a distance less than *d*.

The Getis-Ord Gi statistic* (Getis-Ord, 1992) was computed as follows:

$$G_i^*(d) = \frac{\sum_{j=1}^{n} \omega_{ij}(d).x_j}{\sum_{j=1}^{n} x_j} \qquad \text{(Ord \& Getis, 1995)}$$

A matrix was constructed with standardized values, and based on this matrix, a hierarchical cluster analysis was performed for the three periods as a whole. This made it possible to use the aggregation method to detect groups that behaved homogeneously concerning the segment, which resulted in those with the smallest distances in the matrix being grouped. The Euclidean distance to the centroids was measured, which is a method that detects the point at which there is a sharp jump in the distance coefficient. Based on this point, seven homogeneous groups of behavior were identified (Table 1) using SPSS version 23.

For each of the eight variables, a qualitative assessment was performed according to how close or far it was from the mean: very high - above 1 standard deviation; high - between 0 and 1 standard deviation; low - between 0 and -1 standard deviation; and very low - below -1 standard deviation.

Ethical considerations: as previously indicated, secondary data provided by the Ministry of Health (www.gub.uy/ministerio-salud-publica/) were used in the study, considering the study's temporal period and the locality from which the cases originated. However, these data did not allow for individual identification.

RESULTS

In the city, the distribution of the eight variables, as clarified in the methodology, is categorized into very low, low, high, and very high, as depicted in Figure 3. The

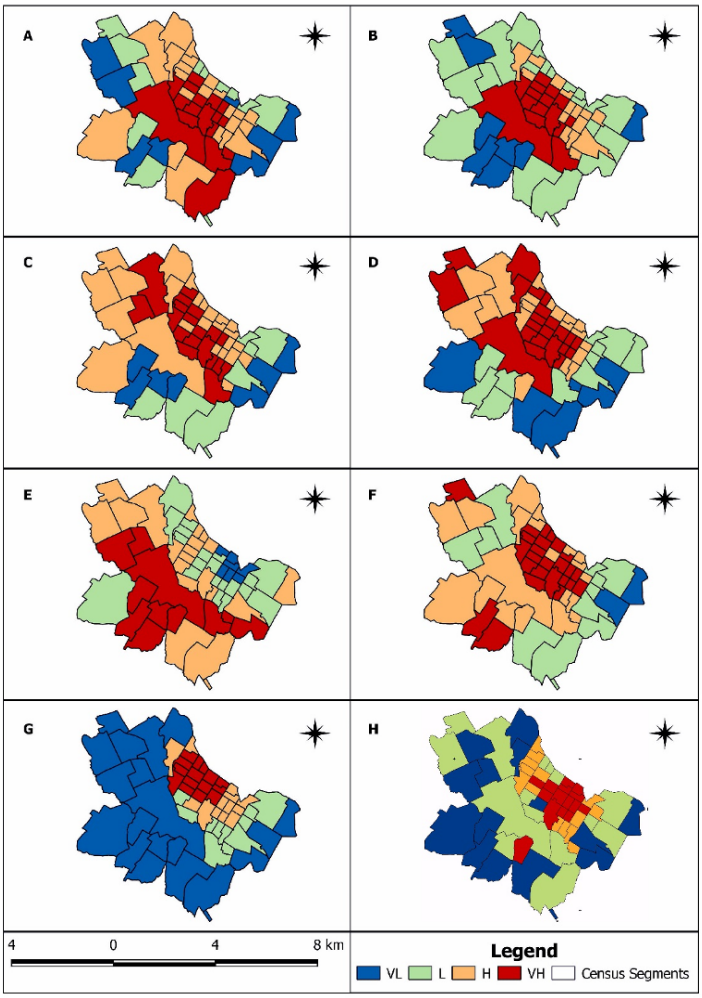

Figure 3. Variables in Rivera based on the categories generated

Legend: (a) distribution of cases in period one; (b) distribution of cases in period two; (c) distribution of cases in period three; (d) mobility in period one; (e) mobility in period two; (f) mobility in period three; (g) population density; (h) socioeconomic index.

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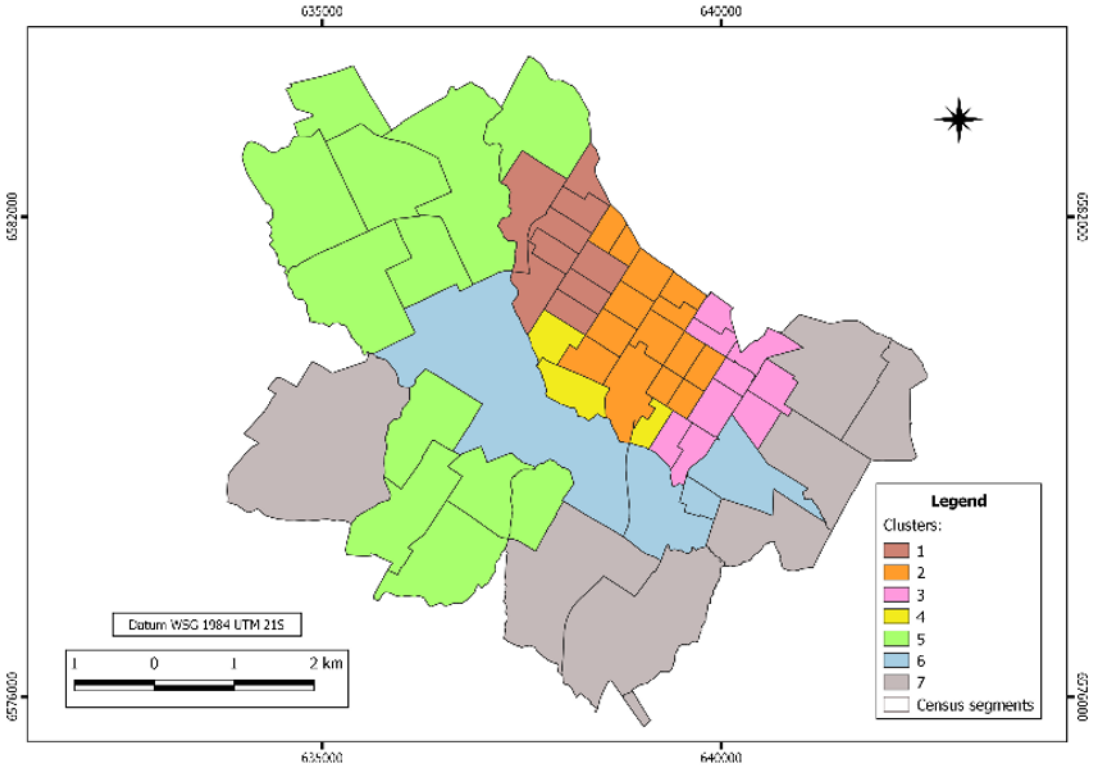

Figure 4. Homogeneous groups in hierarchical analysis of census segments, city of Rivera, Uruguay

graphs showcased in the figure illustrate the breakdown of case and mobility variables across periods one, two, and three. Additionally, data on population density and socioeconomic index variables are included.

Throughout the three periods, it was observed that the highest number of reported COVID-19 cases occurred in the central segments. The same pattern was observed for population density. While mobility predominated in the central segments during periods one and three, it was different in period two, where it was higher in the city's periphery. Finally, the highest socioeconomic level was observed in the central segments near the border with Santana do Livramento (Figure 3).

The result of hierarchical cluster analysis is presented, in which seven clusters are observed (Figure 4). It is essential to analyze this figure and table 1 together, as the table provides insight into the different variables and their distribution.

The behavior in each cluster was identified for each of the eight variables. Table 1 illustrates the study's eight descriptive variables, along with their respective spatial clustering combinations. Each descriptive variable is classified into one of four levels, very low, low, high, or very high, as described in table 1. These categories can be seen in greater detail in table 1, which outlines the classification of each variable in the seven groups.

Two major clusters can be seen from these results. One consists of cluster segments one, two and three, which represent areas with high and very high purchasing power and high and very high population density. We call this clustering the high level. The other group contains the segments in clusters five, six and seven, representing areas with low and very low purchasing power and low and very low population density. We call this clustering the low level.

The high level did not present a uniform evolution over the period analyzed. While clusters one and two always had a high number of cases, the number of cases in cluster three started low, continued high and ended low. The explanatory factor for this difference is mobility. Clusters one and two continued to have high and very high mobility, while cluster three had low and very low mobility.

As for the low level group, while contagion in clusters five and seven remained low and very low, cluster six had a consistently high level of contagion. Here a clear pattern of mobility is not observed, since mobility in clusters five and six are identical. What can be observed is that cluster six displays a lower population density compared to clusters five and seven, where a very low population density can be seen. Within the lower level group, a reduced population density contributes to comparatively fewer reported cases.

Table 1. Variables categorized based on homogeneous group, city of Rivera, Uruguay.

	Clusters*						
Variables	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Distribution of cases in period one	H	H	L	VH	L	H	L
Distribution of cases in period two	H	H	H	VH	VL	H	L
Distribution of cases in period three	H	H	L	H	L	H	VL
Mobility in period one	H	H	L	H	L	L	VL
Mobility in period two	L	VL	VL	L	H	H	L
Mobility in period three	H	H	L	VH	L	L	VL
Population density	H	VH	VH	H	VL	L	VL
Socioeconomic index	VH	VH	H	L	VL	L	L
Total cases	**282**	**386**	**275**	**31**	**268**	**195**	**409**

*Legend: *VH - very high, H – high, L – low, VL - very low.*

DISCUSSION

The distribution of groups in different spaces is influenced by social, cultural, and environmental factors, which manifest in how people utilize these spaces. The variables selected by the study herein made it possible to represent, in part, this expression and to explain differences in how the disease behaved in areas that had greater and fewer number of cases. The territorial level of analysis was based on the greatest degree of detail available, namely, the administrative units (census segments). Local homogeneity in behavior was found when clustering the census segments.

In areas characterized by a high socioeconomic level, mobility appeared to be the key variable in explaining the differences in case numbers. These areas were primarily located in the downtown commercial region closest to the border street connecting Rivera and the city of Santana do Livramento, Brazil. These clusters, labeled as one and two, represented areas that were susceptible to the introduction of new variants due to the significant interdependence between residents on both sides of the border.[20] This is particularly relevant for border cities, where interactions and exchanges between neighboring populations play a substantial role.[20,21]

However, for areas with a low socioeconomic level, it was observed that clusters with the fewest number of cases (clusters five and seven) exhibited very low population density. Interestingly, even when there was increased mobility during certain periods, the number of cases remained low in these areas. This finding could be attributed to a very low population density

Meanwhile, a greater presence of cases was found in the most densely populated areas of Rivera where there was daily migration associated with a porous border.[21] While it has not been physically possible to completely close this border, authors[22] also point out that such a closure could lead to the use of alternative routes of entry, which would result in a greater risk to the population. Another study of a binational border,[23] where there was daily migration of agricultural workers, found that health care could be received on both sides of the border.

The higher incidence of cases in more densely populated areas is consistent with previous research highlighting the association between population density and the spread of the disease.[11, 12, 24, 25] This study emphasizes the importance of considering population density as a significant factor for areas with a low socioeconomic level. Previous studies have also indicated the relevance of socioeconomic level in relation to the number of cases.[16, 26] However, it should be noted that the relationship between the behavior of the number of cases and socioeconomic level is not uniformly consistent.[11,24] Higher indicators in areas with a higher socioeconomic level can sometimes be attributed to better detection[24] of capabilities and individuals' ability to practice isolation, resulting in lower indicators.[27]

While socioeconomic level should be considered, it is essential to also consider factors such as density and mobility when predicting indicators.

In the present study, clusters one and two exhibited high mobility, particularly during the initial weeks. Contrary to some claims that restricting mobility has limited effectiveness in reducing the number of cases,[15, 22] this exploratory study found a positive association between increased mobility and incidence of cases.[28]

The geo-statistical analysis presented herein is considered to be a strength of this work, given that conventional models have been known to be biased because they produce averages without considering geographic variability.[27] Working at the greatest level of detail possible, as done in this study, allows for identifying specific spatial patterns, and is especially important when analyzing border-specific phenomena.[24] Another strength of this work is that it used socioeconomic information that was analyzed at the level of the census segment.[12]

Furthermore, a study that used a broad scoping review (n=95) argued that most of the research presents data at the district/county level, unlike the study presented herein, which uses microdata. Therefore, this can be considered a better proxy for individual situations.[29]

However, there are limitations to consider. Mobility data did not differentiate statistically between the "residence" category and other categories. Some authors argue that different events occurring in residential areas can result in close proximity among individuals and should not receive distinct treatment.[13] Additionally,

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mobility data only represent individuals who agreed to provide such information and used the Android system.[30]

As an exploratory study based on secondary data, causality and temporality cannot be determined.[31] Therefore, further research is needed to analyze the social-environmental heterogeneity and mobility within cities, incorporating other environmental variables such as the presence of green space.[32]

Based on the results, it is concluded that priority should be given to areas in the city of Rivera with higher population density and greater mobility. These findings can inform the community in controlling the disease, guide the design of effective public policies, and allocate resources based on scientifically grounded priority criteria, thereby improving effectiveness.[33] Furthermore, given the recognition of the importance of the migration condition, the surveillance system should include socio-environmental variables that also consider the migration condition as a variable to be studied.[29]

To prepare the system for future epidemic situations, health system inequities should also be addressed. This would improve community resilience[34] and deepen ties among binational policies.

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AUTHORS' CONTRIBUTIONS

Marcel Achkar, conception and design of the work, collection/obtaining results, data analysis and interpretation, drafting the manuscript, critical review of the manuscript, approval of the final version. **Mariana Gómez-Camponovo**, conception and design of the work, collection/obtaining results, data analysis and interpretation, drafting the manuscript, critical review of the manuscript, approval of the final version. **Nicolas Pérez**, conception and design of the work, data analysis and interpretation, drafting the manuscript, critical review of the manuscript, approval of the final version. **Eleuterio Umpiérrez**. conception and design of the work, data analysis and interpretation, critical review of the manuscript, approval of the final version.

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ORIGINAL ARTICLE

HIV and childhood tuberculosis: fragmentation of the flow of information in the countryside of the state of São Paulo

HIV e tuberculose infantil: a fragmentação do fluxo de informação no interior paulista

VIH y tuberculosis infantil: la fragmentación del flujo de información en el interior del estado de São Paulo

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Corresponding Author:
Thamires Carraro Gatto
thamiresgatto@estudante.ufscar.br

Adress: Rodovia Washington Luís, km 235, SP-310, São Carlos, São Paulo, Brasil.

Thamires Carraro Gatto[1];
Giovana Cristina Chirinéa Donida[1];
Eliza Flori Rodrigues da Costa[2];
Monika Wernet[1];
Mellina Yamamura[1];

[1] *Universidade Federal de São Carlos, São Carlos, São Paulo, Brasil.*
[2] *Universidade de São Paulo, Ribeirão Preto, São Paulo, Brasil.*

ABSTRACT

Background and objectives: children are still affected by HIV and tuberculosis (TB). This study aimed to identify the occurrence of HIV and TB cases in children. **Methods:** this is an epidemiological, non-experimental, retrospective study, in which the population was made up of records of HIV and TB cases in children living in a municipality in the countryside of the state of São Paulo, from 2012 to 2022, in the age group of zero to 13 years old. After data collection, data consistency and validity was checked, followed by categorization of information for descriptive analyses and presentation in absolute and relative frequency tables. **Results:** during the study period, six HIV cases and seven TB cases were identified in children with a respective average annual incidence of 0.033 and 0.031 cases/1,000 inhabitants aged up to 13 years. There were 146 notifications of HIV-exposed children. There was a difference of months to years between the dates of diagnosis and notification, which deviates from the Ministry of Health recommendations. Incompatibility was found between municipal and state registration platforms, which shows a breakdown in flow of information on notifications. **Conclusion:** there have been HIV and childhood TB cases in the last ten years. Structural problems were identified in the fragmentation of the flow of information that subsidizes health actions according to the population's needs, which overshadows the health system's ability to respond.

Keywords: *Human Immunodeficiency Virus. Tuberculosis. Child Health. Neglected Diseases.*

RESUMO

Justificativa e Objetivos: crianças ainda são afetadas pelo HIV e pela tuberculose (TB). Dessa forma, o objetivo do estudo foi identificar a ocorrência de casos de HIV e TB em crianças. **Métodos:** trata-se de estudo epidemiológico, não experimental, retrospectivo, em que a população foi constituída pelo registro de casos infantis de HIV e TB residentes em um município do interior do estado de São Paulo, no período de 2012 a 2022, na faixa etária de zero a

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13 anos de idade. Após a coleta de dados, foi realizada a verificação de consistência e validade dos dados, seguida do tratamento categorizado das informações para análises descritivas e apresentação em tabelas de frequência absoluta e relativa. **Resultados:** no período de estudo, foram identificados seis casos de HIV e sete de TB em crianças com média anual respectiva de 0,033 e 0,031 casos/1.000 habitantes com idade até 13 anos. Verificaram-se 146 notificações de criança exposta ao HIV. Houve diferença de meses a anos entre as datas de diagnóstico e de notificação, o que diverge do recomendado pelo Ministério da Saúde. Foi verificada a incompatibilidade entre plataformas de registro de âmbito municipal e estadual, o que evidencia uma quebra do fluxo de informação das notificações. **Conclusão:** houve ocorrência de casos de HIV e TB infantil nos últimos dez anos. Foram identificados problemas estruturais na fragmentação do fluxo da informação que subsidia ações de saúde de acordo com as necessidades da população, o que ofusca a capacidade de resposta do sistema de saúde.

***Descritores**: Vírus da Imunodeficiência Humana. Tuberculose. Saúde da Criança. Doenças Negligenciadas.*

RESUMEN

Antecedentes y Objetivos: los niños siguen estando afectados por el VIH y la tuberculosis (TB). El objetivo de este estudio fue identificar la ocurrencia de casos de VIH y TB en niños. **Métodos:** se trata de un estudio epidemiológico, no experimental, retrospectivo, en el cual la población fue constituida por los registros de casos de VIH y TB en niños residentes en un municipio del interior del estado de São Paulo entre 2012 y 2022, con edad entre cero y 13 años. Después de la recolección de datos, se verificó la consistencia y validez de los mismos, seguido del tratamiento categorizado de la información para análisis descriptivos y presentación en tablas de frecuencias absolutas y relativas. **Resultados:** durante el periodo de estudio, se identificaron seis casos de VIH y siete de TB en niños, con una incidencia media anual respectiva de 0,033 y 0,031 casos/1.000 habitantes de hasta 13 años. Hubo 146 notificaciones de niños expuestos al VIH. Hubo una diferencia de meses a años entre las fechas de diagnóstico y notificación, lo que se desvía de lo recomendado por el Ministerio de Salud. Hubo incompatibilidad entre las plataformas de registro municipal y estatal, lo que muestra una ruptura en el flujo de información sobre las notificaciones. **Conclusión:** se han registrado casos de VIH y de tuberculosis infantil en los últimos diez años. Se identificaron problemas estructurales en la fragmentación del flujo de información que subvenciona las acciones sanitarias según las necesidades de la población, lo que ensombrece la capacidad de respuesta del sistema sanitario.

***Palabras Clave:** Virus de la Inmunodeficiencia Humana. Tuberculosis. Salud Infantil. Enfermedades Olvidadas.*

INTRODUCTION

Tuberculosis (TB) and the human immunodeficiency virus (HIV), the etiological agent of Acquired Immunodeficiency Syndrome (AIDS), are transmissible diseases that still maintain high incidence rates, as despite scientific advances related to the prevention and treatments of both, are neglected infections. In fact, eliminating these public health problems by 2030 is one of the health and well-being goals of the Sustainable Development Goals (SDGs), established by the Pan American Health Organization (PAHO).[1]

In Brazil, between 2021 and 2022, 40,880 new HIV cases and 78,057 TB cases were reported, respectively, across the entire population, regardless of age group.[2,3] Therefore, co-infection between them is common, since people living with HIV are 20 times more susceptible to acquiring TB than individuals who do not live with the virus, which is evidenced by increased co-infection in the country in the last ten years.[4]

Aware that the incidence of these diseases in the child population is related to the prevalence in the adult population, when directing attention to children affected by these infections, the situation is more worrying, since children are prone to developing severe forms of these diseases. In 2020, it was estimated that there were 300,000 children living with the HIV virus and another 120,000 children died from AIDS-related causes worldwide.[5]

Inherent to aspects of TB, a large proportion of children affected by this infection, especially those under five years old, acquired the disease through living with people infected with TB.[6] In Brazil, 2,703 new TB cases were registered in this population in 2022 alone.[3]

In line with the facts mentioned above, it must be considered that childhood pulmonary TB has common manifestations, which can be confused with other conditions, such as pneumonia or malnutrition.[7] Furthermore, up to 20.0% of pediatric TB cases are extrapulmonary, which makes diagnosis even more difficult.[6]

Despite all the challenges faced by the health system in controlling preventable diseases and managing these communicable chronic conditions, there were also other impacts generated by the coronavirus pandemic (COVID-19). Syndemic interaction with other emerging and neglected infectious diseases and sociocultural weaknesses have increased the challenges in controlling various diseases, even causing environmental damage.[8]

It is estimated that the interference of the COVID-19 pandemic resulted in the interruption of 63.0% of prenatal care tests, 59.0% of postnatal tests, a drop in care services for sick children and an increase in malnutrition. As a result, HIV and TB diagnoses, notifications, treatments and prevention have also been affected in recent years.[9]

Thus, it is estimated that 800 thousand HIV-positive children left treatment during the pandemic period, Moreover, a third of children born to mothers living with HIV were not tested, and 50.0% of children with HIV died before of the second birthday in the same time interval.[10]

It was no different with TB, as there was a large reduction in those diagnosed in 2019 and 2020, which reflected in a 16.0% decrease in notifications in that period. However, the number of treatments also decreased, resulting in an increase in TB deaths, as, at the time of the pandemic, there was a regression to 2017 levels, with 1.3 million TB deaths among HIV-negative and 214,000 among HIV-positive.[2]

Therefore, in order to understand the epidemiology of these infections in the Brazilian population and, specifically, in the municipality considered a technological hub in the state of São Paulo, this study aimed to identify the occurrence of HIV and TB cases in children.

METHODS

This is an epidemiological, non-experimental, retrospective study, in which people are selected without considering the state of exposure or disease, i.e., exposure is investigated simultaneously with the disease.[11]

The municipality where the study was carried out is in the center of the state of São Paulo (SP). It constitutes approximately 0.4% of the territory and 0.6% of the total population of the state, which is made up of 645 municipalities, divided into 15 mesoregions, totaling an area of 248,219.485 km², considered the most populous state in the country, with 44,420,459 inhabitants. Furthermore, it has a high rate of economic development, with a Human Development Index of 0.805.[12]

The research population consisted of notifications of childhood HIV cases, children exposed to HIV and TB, living in a rural municipality in the state of SP, from 2012 to 2022, in the age group from zero to 13 years old. This age group is justified by the operationalization of HIV data that are separated into children under 13 years old and over 13 years old, precisely due to the specificities of the disease.

Notified HIV cases in children under 13 years old and records of children exposed to HIV of residents in the research setting were obtained from the Notifiable Diseases Information System (SINAN - *Sistema de Informação de Agravos de Notificação*). TB cases with the same characteristics were collected in the Tuberculosis Patient Control System in São Paulo (TBWeb - *Sistema de Controle de Pacientes com Tuberculose no Estado de São Paulo*). Furthermore, municipal population data from the free access platform of the Brazilian Institute of Geography and Statistics (IBGE - *Instituto Brasileiro de Geografia e Estatística*) were considered. Data collection took place on February 10, 2022.

After data collection, three separate spreadsheets were created using Microsoft Excel® for each problem. Subsequently, the data underwent validity and treatment of variables, coding the categories into real numbers and building a code record (Code Book). In this process, the research eligibility criteria were also applied, "records outside the specified period, with dates of birth over 13 years old and residences different from the research scenario were excluded".

Sequentially, a descriptive data analysis was carried out, with calculations of minimum, maximum values and measures of central tendency (mean) for continuous quantitative variables of age and interval in days between the date of diagnosis and the date of notification. To present the data, absolute and relative frequency tables were constructed. To calculate the average annual incidence rate for HIV and TB cases, the criteria in the equation below were considered:

$$Tx = \frac{Yi}{Pi} \div Ti \times 1{,}000\ inhabitants$$

Thus, *Tx* represented the incidence, *Yi*, the number of cases registered according to established criteria, *Pi*, estimated exposed population from zero to 13 years with logarithmization of 13.0%, due to estimated population growth from 2010 to 2022, and *Ti*, time. Four and five years were considered to calculate HIV and TB cases, respectively, according to the incidence dates from 2012 to 2022.

In accordance with the rules contained in Resolution 466/2012, this research project was submitted and approved by the Research Ethics Committee on December 21, 2022, under Certificate of Presentation for Ethical Consideration (*Certificado de Apresentação para Apreciação Ética*) 66090722.6.0000.5504 and Opinion 5.833.876.

RESULTS

From 2012 to 2022, eight HIV cases in children under 13 years old and seven of childhood TB were identified in the municipality under study on the SINAN and TBWeb platforms, respectively. However, in the case of HIV cases, two of them were excluded.

Regarding HIV cases in children under 13 years old, it was identified that all were caused by vertical transmission. For this reason, mother demographic characteristics were observed, which are predominantly composed of women aged 21 to 30 years (n= 3; 50.0%), with only two of them aged between 31 and 40 years (33.0%) and one from 41 to 50 years old (17.0%). Furthermore, mothers declare themselves to be white or brown, with an equal distribution between both races/colors, with a low level of education, since three (50.0%) of them had incomplete elementary education, two (33.0%) had incomplete high school and only one (17.0%) completed high school.

Concerning childhood TB, there was a greater diversity of tests performed concomitantly for TB diagnosis when compared to the adult population. Thus, one (14.2%) case was diagnosed with TB after smear microscopy and X-ray, one (14.2%) after X-ray and

culture, one (14.2%) with smear microscopy alone, one (14.2%) by histopathological analysis and two (29.0%)

only by X-ray.

Finally, an intriguing fact would be that one case (14.2%) was reported as TB, but without specification of the diagnostic method, adding that this case presented a clinical form of the disease classified as extrapulmonary. Furthermore, it is worth noting that in no case was a sensitivity test performed and only six (86.0%) underwent a rapid HIV test, in order to investigate the existence of co-infections, in which all presented a negative result (Table 1).

Table 1. Description of HIV and tuberculosis cases in children under 13 years old according to the variables analyzed in SP, Brazil, 2023

	HIV in < 13 years old						TB in <13 years old					
	Male		Female		Total		Male		Female		Total	
Variables	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Year of incidence (date of diagnosis)												
2012	1	100.0	0	0.0	1	100.0	1	100.0	0	0.0	1	100.0
2013	0	0.0	0	0.0	0	0.0	1	100.0	0	0.0	1	100.0
2015	0	0.0	2	100.0	2	100.0	0	0.0	1	100.0	1	100.0
2016	1	50.0	1	50.0	2	100.0	0	0.0	0	0.0	0	0.0
2018	0	0.0	0	0.0	0	0.0	2	100.0	0	0.0	2	100.0
2019	0	0.0	1	100.0	1	100.0	0	0.0	0	0.0	0	0.0
2020	0	0.0	0	0.0	0	0.0	2	100.0	0	0.0	2	100.0
Total for the period	2	33.0	4	67.0	6	100.0	6	86.0	1	14.0	7	100.0
Age range												
0-2	0	0.0	2	33.0	2	33.0	2	29.0	0	0.0	2	29.0
3-5	1	17.0	2	33.0	3	50.0	1	14.0	0	0.0	1	14.0
6-8	1	17.0	0	0.0	1	17.0	0	0.0	0	0.0	0	0.0
9-11	0	0.0	0	0.0	0	0.0	1	14.0	0	0.0	1	14.0
12-13	0	0.0	0	0.0	0	0.0	2	29.0	1	14.0	3	43.0
Race/color												
White	2	33.2	3	49.8	5	83.0	2	29.0	1	14.0	3	43.0
Brown	0	0.0	1	17.0	1	17.0	4	57.0	0	0.0	4	57.0
Clinical form of tuberculosis												
Pulmonary	NA	NA	NA	NA	NA	NA	4	57.0	0	0.0	4	57.0
Extrapulmonary	NA	NA	NA	NA	NA	NA	2	29.0	1	14.0	3	43.0
Type of closure												
In treatment	1	15.7	3	50.2	4	67.0	0	0.0	0	0.0	0	0.0
Cure	NA	NA	NA	NA	NA	NA	6	74.0	1	12.0	7	86.0
Abandonment	0	0.0	0	0.0	0	0.0	1	7.0	0	7.0	1	14.0
Death not related to the injury	1	16.5	1	16.5	2	33.0	0	0.0	0	0.0	0	0.0
Interval in days between the date of diagnosis and the date of notification in total cases												
More than 1095 days	1	16.6	0	0.0	1	16.6	0	0.0	0	0.0	0	0.0
731 to 1095 days	0	0.0	1	16.6	1	16.6	0	0.0	0	0.0	0	0.0
366 days to 730 days	0	0.0	1	16.6	1	16.6	0	0.0	0	0.0	0	0.0
91 to 365 days	1	16.8	1	16.8	2	33.6	0	0.0	0	0.0	0	0.0
30 to 90 days	0	0.0	1	16.6	1	16.6	1	7.0	0	7.0	1	14.0
Up to 7 days	0	0.0	0	0.0	0	0.0	3	43.0	0	0.0	3	43.0
0 days	0	0.0	0	0.0	0	0.0	2	29.0	1	14.0	3	43.0

Source: survey data. Caption: NA - not applicable.

As for the average annual incidence rate, it was possible to observe 0.033 cases per 1.000 inhabitants aged 0 to 13 years for HIV and 0.031 cases per 1.000 inhabitants aged 0 to 13 years for TB.

Furthermore, regarding the context of HIV cases in children under 13 years old, it was possible to identify on this same platform, SINAN, 146 notifications of children exposed to HIV, in which 28 records were excluded due to incompatibility of the municipality of residence and age in relation to established criteria, following only 118 records for descriptive analysis. There was a considerable time interval between the date of diagnosis and the date of notification, since only three (3.0%) were registered on the same day, 87 (74.0%) took up to eleven months, 17 (14.0%) took from one to five years and 11 (9.0%) were notified only after five years.

In relation to the demographic characteristics of these children, males stood out, with 63 (53.0%) of them

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and 55 (47.0%) of females. Furthermore, are mostly white, accounting for 83 (71.0%) of the records, followed by brown race/color (n=18; 15.0%) and black (n= 6; 5.0%), whereas in 11 (9.0%) records race/color statement was ignored. Finally, in relation to age group, 106 (90.0%) of them are between zero and two years old, five (4.0%) are between three and five years old and seven (6.0%) are between six and eight years.

DISCUSSION

The study sought to identify the occurrence of childhood HIV and TB cases in the municipality of rural São Paulo, from 2012 to 2022, with the aim of calculating the incidence rate of HIV and TB in the pediatric population and analyzing the demographic characteristics of children affected by these grievances.

Therefore, the existence of HIV and TB cases in children under 13 years old deserves attention, as it mostly reflects failures in the care provided to parents and adults who live with these children. Thus, the research shows that, despite the advances and strengthening of the Brazilian Health System (SUS – *Sistema Único de Saúde*), through the implementation of new free therapeutic schemes and greater control and intensification of epidemiological surveillance actions, there are still limitations, including scientific knowledge, for an effective improvement in communicable disease prevention and control,[13] as expected by the SDG goals.[1]

Furthermore, the political-institutional situation in force as of 2018 undermined the public health advances achieved in recent years, through reduced funding, failure to promote science and new projects, which intensified with the COVID-19 pandemic.[13,14] Thus, the predominance of HIV and TB cases in this age group makes up the representation of a SUS that, during the COVID-19 pandemic, was approached as a constitutional SUS, a problem SUS, a disputed SUS and an active SUS, but which, regardless of its context, aims to universalize access to health care services. However, for SUS to be able to act in accordance with its essential nature, it is necessary to expand and improve the scope of surveillance, prevention and control of diseases and health risks.[13]

In this regard, some specific initiatives in the field of HIV have already been implemented, such as the Brazilian National Pact for Vertical Transmission Elimination guidelines, which involves the services offered by Primary Health Care (PHC), directing prenatal care, postpartum monitoring, prophylactic measures, adequate treatment and health surveillance actions in accordance with the best scientific evidence and specificities. Furthermore, they encourage adherence to measures by health services through awards, such as the implementation of the HIV and/or Syphilis Vertical Transmission Elimination Certification.[15]

As for the demographic aspects of cases of both diseases, regarding race/color and sex, it is worth mentioning that there was no difference in what is already evidenced in scientific literature.[2] However, a worrying aspect was the age range of TB cases, since there were cases in children up to two years old (29.0%) and between three and five years old (14.0%), which generates greater concern regarding symptoms and diagnosis of the disease.[7]

Therefore, when considering the intrinsic relationship between the incidence of childhood TB and the prevalence of TB in adults, numerous hypotheses are raised about follow-up of epidemiological surveillance for this population, such as failures in diagnosis, contact screening and non-adherence to preventive TB treatment.[16] This scenario reflects and reinforces inequality in access to health services, which is became even more latent with the COVID-19 pandemic.[17]

Furthermore, regarding the clinical form of TB, all were new cases, most of which were pulmonary TB (57.0%), but there was a higher quantity of extrapulmonary TB (43.0%) than expected, as, when observing cases of childhood TB across the country, Brazil, only 19.4% of them are characterized by the extrapulmonary clinical form.[3]

Considering the diagnostic difficulties, due to the greater variation in clinical and symptomatological forms and the smaller number of bacilli than adults,[18] diversity was observed in relation to exams; in fact, many of the cases (43.0%) were diagnosed after two tests. Furthermore, it was observed that almost everyone (57.0%) used the X-ray exam, which is assertive, as most children develop radiological signs of TB infection,[6] while only one underwent a smear test only (14.2%).

Furthermore, one of the cases of extrapulmonary TB (14.2%) had a negative result for smear microscopy, and no other tests were performed. It is believed that other tests were carried out, focusing on the organ affected by the disease.[6]

Finally, it was possible to analyze that the cure rate for childhood TB in the city was 86.0%, compatible with that recommended by the WHO.[2] Despite the encouraging estimate, one cannot fail to highlight the episode of abandonment, which was becomes extremely worrying, as interrupting treatment can worsen the situation.[19]

At the same time, the lack of access to health promotion and prevention information is also strongly highlighted from the analysis of HIV cases, since they all occurred through vertical transmission, which reveals the non-adherence to treatment by a large number of pregnant women living with HIV. However, this is also a reflection of the lack of implementation of the protocol of good practices and adequate reception by the health service, which results in negligence and abandonment in relation to treatment.[20]

Although transmissions to this audience are mostly vertical, it must be remembered that children in vulnerable situations are exposed to other forms of infection, through risky sexual relations and piercing with contaminated needles in unhealthy places, for instance. [21]

In this sense, in conjunction with the various factors related to monitoring these cases, there is the possibility of greater detail with the notification of children exposed to HIV. However, much important information is not cov-

ered by SINAN, due to a lack of updating, which prevents the analysis of important variables and the outcome of the case, generating greater susceptibility to underreporting.[22]

Another factor that deserves to be highlighted is the large time interval between the date of exposure and the date of notification on SINAN, since very few were registered on the same day (3.0%), while the majority took up to 11 months (74.0%) and, even, some of them took more than five years to do so (9.0%). These extended periods contradict what is recommended by the Ministry of Health (MoH), as it is determined that the notification forms of children exposed to HIV are registered in SINAN within a maximum of seven days, in order to ensure the monitoring of these children.[22]

This delay in SINAN notification also occurred in relation to HIV disease in children under 13 years old, with no case being reported on the same day or in the same week, as advised by the MoH[22], with the minimum notification interval varying between one and three months (16.0%), whereas the maximum was more than two years (16.0%). This is detrimental to the functioning of the units that provide assistance to this population and carry out epidemiological surveillance of these diseases, because it is based on the number of cases registered in SINAN that the funds for the Fixed Health Surveillance Floor (FHSF) and the Variable Health Surveillance Floor (VHSF) necessary to maintain the service are calculated.[23]

Thus, a break in the information flow of notification of these cases was proven, as, after carrying out a free search of HIV cases in children under 13 years old in the city under analysis on the São Paulo STD/AIDS Reference and Training Center platform (CRT - *Centro de Referência e Treinamento DST/AIDS*), only two records of this problem were found in the municipality under study in the last ten years, one in 2015 and one in 2019, while, in fact, according to the data collected in this research, there were six cases, i.e., four of them are not included in the CRT system, incidents in 2012, 2015 and 2016.

Knowing that this data from the CRT platform is fed by the Regional Health Departments in partnership with the State Department of Health, it is clear that there was a break in the flow of information provided for Health Care Networks (RAS - *Redes de Atenção à Saúde*). These aspects corroborate the idea that there is a diversity of meanings attributed to SUS[17], such as the effects we identified in this research as structural problems in the fragmentation of the flow of information responsible for supporting health actions according to the population's needs.

Scenarios like this obfuscate the system's responsiveness. On the other hand, only through these materials is it possible to mobilize investment prospects, strengthening and recognition of a health system considered a crucial national heritage, which has already overcome several obstacles and transformed into a historic enterprise recognized worldwide.[17]

It is worth mentioning that this study has limitations, due to the use of secondary data and the research design itself, as it is a descriptive study that does not allow for relationship analyzes to be carried out. However, it provided hypotheses for future studies.

Thus, hypotheses are raised about the repetition of this circumstance in other municipalities and states, as services can take this experience as a strategy for validating its epidemiological data and, consequently, contributing to the decrease in national underreporting, which undermines and the reliability of epidemiological bulletins of this disease.[2]

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AUTHORS' CONTRIBUTIONS:

Thamires Carraro Gatto contributed to bibliographical research, writing the abstract, introduction, methodology, discussion, interpretation and description of results, preparation of tables, conclusions, review and statistics. **Giovana Cristina Chirinéa Donida** contributed to writing the abstract, introduction, methodology, discussion, interpretation and description of results, conclusions, review and statistics. **Eliza Flori Rodrigues da Costa** contributed to analysis and interpretation of results and writing of discussion. **Monika Wernet** contributed to writing the introduction, methods and discussion. **Mellina Yamamura** contributed to project administration, fund acquisition, literature research, results analysis and discussion, 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.

PUBLICAÇÃO OFICIAL DO NÚCLEO HOSPITALAR DE EPIDEMIOLOGIA DO HOSPITAL SANTA CRUZ E PROGRAMA DE PÓS GRADUAÇÃO EM PROMOÇÃO DA SAÚDE - DEPARTAMENTO DE BIOLOGIA E FARMÁCIA DA UNISC

Revista de Epidemiologia e Controle de Infecção

Hospital Santa Cruz

ORIGINAL ARTICLE

Antimicrobial prescription and bacterial resistance in a Brazilian Intensive Care Unit

Prescrição antimicrobiana e resistência bacteriana em uma Unidade de Terapia Intensiva Brasileira

Prescripción antimicrobiana y resistencia bacteriana en una Unidad de Cuidados Intensivos Brasileña

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Corresponding Author:
Lucia Collares Meirelles
luciacmeirelles@gmail.com

Address: Rua São Luis, 150, Anexo I Faculdade de Farmácia, Porto Alegre, Rio Grande do Sul, Brazil

Lucia Collares Meirelles[1];
Vera Lúcia Milani Martins[2];
Diogo Pilger[1];

[1] *Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil.*
[2] *Instituto Federal de Educação, Ciência e Tecnologia do Rio Grande do Sul, Porto Alegre, RS, Brazil.*

ABSTRACT

Background and Objectives: antimicrobial resistance is one of the main public health concerns worldwide. Intensive Care Units have a high prevalence of resistant microorganisms and infections, and the rational use of antibiotics is one of the main strategies for tackling this problem. This work aimed to describe patterns associated with antimicrobial drugs as well as the resistance profile of microorganisms. **Methods:** an observational study was carried out using data from patients hospitalized in the Intensive Care Unit who used antimicrobial agents. **Results:** respiratory and cardiological causes were the most frequent reasons for admission, with cephalosporins (29.02%), with penicillin (25.84%) and macrolides (16.10%) being the most used classes of antibiotics. The predominant microorganisms were *Klebsiella pneumoniae* (13.98%), *Staphylococcus aureus* (13.44%) and *Acinetobacter baumannii* (11.83%). Urine cultures and tracheal aspirate were the culture tests with the highest growth of gram-negative microorganisms. Patients with bacteria isolated in tracheal aspirate had longer hospital stays; 20 patients had positive surveillance cultures; and the mortality rate found was 55.45%. **Conclusion:** the study combined the institution's epidemiological profile with patient characteristics, isolated microorganisms and outcomes.

Keywords: *Anti-Bacterial Agents. Drug Resistance, Microbial. Intensive Care Units. Laboratory Test.*

RESUMO

Justificativa e Objetivos: a resistência antimicrobiana é uma das principais preocupações de saúde pública em todo o mundo. As Unidades de Terapia Intensiva têm uma alta prevalência de microorganismos resistentes e infecções, e o uso racional de antibióticos é uma das principais estratégias para lidar com esse problema. Este trabalho teve como objetivo descrever padrões associados a medicamentos antimicrobianos, bem como o perfil de

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resistência dos microorganismos. **Métodos:** foi realizado um estudo observacional utilizando dados de pacientes hospitalizados na Unidade de Terapia Intensiva que utilizaram agentes antimicrobianos. **Resultados:** causas respiratórias e cardiológicas foram os motivos mais frequentes de admissão, com cefalosporinas (29,02%), penicilina (25,84%) e macrolídeos (16,10%) sendo as classes de antibióticos mais utilizadas. Os microorganismos predominantes foram *Klebsiella pneumoniae* (13,98%), *Staphylococcus aureus* (13,44%) e *Acinetobacter baumannii* (11,83%). Culturas de urina e aspirado traqueal foram os testes de cultura com maior crescimento de microorganismos gram-negativos. Pacientes com bactérias isoladas no aspirado traqueal tiveram internações mais longas; 20 pacientes tiveram culturas de vigilância positivas; e a taxa de mortalidade encontrada foi de 55,45%. **Conclusão:** o estudo combinou o perfil epidemiológico da instituição com características dos pacientes, microorganismos isolados e resultados.

Palavras-chave: *Agentes Antibacterianos. Resistência Microbiana a Medicamentos. Unidades de Terapia Intensiva. Testes Laboratoriais.*

RESUMEN

Antecedentes y Objetivos: la resistencia antimicrobiana es una de las principales preocupaciones de salud pública en todo el mundo. Las Unidades de Cuidados Intensivos tienen una alta prevalencia de microorganismos resistentes e infecciones, y el uso racional de antibióticos es una de las principales estrategias para abordar este problema. Este trabajo tuvo como objetivo describir patrones asociados con medicamentos antimicrobianos, así como el perfil de resistencia de los microorganismos. **Métodos:** se llevó a cabo un estudio observacional utilizando datos de pacientes hospitalizados en la Unidad de Cuidados Intensivos que utilizaron agentes antimicrobianos. **Resultados:** las causas respiratorias y cardiológicas fueron las razones más frecuentes de admisión, con cefalosporinas (29,02%), penicilina (25,84%) y macrólidos (16,10%) siendo las clases de antibióticos más utilizadas. Los microorganismos predominantes fueron *Klebsiella pneumoniae* (13,98%), *Staphylococcus aureus* (13,44%) y *Acinetobacter baumannii* (11,83%). Los cultivos de orina y el aspirado traqueal fueron las pruebas de cultivo con mayor crecimiento de microorganismos gramnegativos. Los pacientes con bacterias aisladas en el aspirado traqueal tuvieron estancias hospitalarias más largas; 20 pacientes tuvieron cultivos de vigilancia positivos; y la tasa de mortalidad encontrada fue del 55,45%. **Conclusión:** el estudio combinó el perfil epidemiológico de la institución con las características de los pacientes, los microorganismos aislados y los resultados.

Palabras clave: *Agentes Antibacterianos. Resistencia Microbiana a los Medicamentos. Unidades de Cuidados Intensivos. Pruebas de Laboratorio.*

INTRODUCTION

Antimicrobial resistance has become one of the main public health concerns worldwide.[1,2] Intensive Care Units (ICU) play an important role in this topic, as they have a high prevalence of infections and resistant microorganisms due to several factors, such as the criticality of patients, the use of various invasive devices and the prescription of broad-spectrum antimicrobial agents.[3] The use of antibiotics is essential in combating infections, however their irrational use can lead to the adaptation of microorganisms and bacterial resistance.[4,5] There is a need for caution when using them, since indiscriminate use can lead to resistance, and nosocomial infections caused by resistant microorganisms are important causes of mortality and morbidity in hospitalized patients.[6]

The global epidemiological profile of infections in ICUs is already known.[7,8] The prescription patterns of antimicrobial agents adopted in ICUs as well as the resistance profile of pathogens vary widely. However, studies on the use of medications are important tools for understanding how they are prescribed and used. For the class of antimicrobial agents, the studies make it possible to visualize the prescription pattern, being able to relate it to the types of infection, microorganisms and patient outcomes. These data help to support the development of policies, contributing to the development of actions aimed at the rational use of antimicrobial agents, which is one of the main goals for reducing infections caused by multi-resistant microorganisms. Associated with this, the financial resources required by an ICU are high, and antimicrobial agents are high-cost medications, requiring up to 30% of the total spent by patients during admission.[9]

The work aimed to describe patterns associated with antimicrobial drugs as well as the resistance profile of microorganisms.

METHODS

This is a cross-sectional study, with retrospective data collection of patients admitted to the ICU using antimicrobial agents, carried out between January 1 and December 31, 2019. The ICU analyzed in this study is located in a tertiary hospital specialized in trauma-orthopedics with ten general adult ICU beds in the city of Porto Alegre, Brazil.

Data from all adult patients who received antimicrobial agents, enterally or parenterally, during their ICU stay were included. Consecutive readmissions were considered as new cases. Data from patients hospitalized for immediate postoperative recovery and with a length of stay of less than 48 hours were excluded.

Demographic and clinical data were collected from patients' electronic medical record, such as age, sex, city of origin, comorbidities, length of stay in the ICU and hospital, Body Mass Index (BMI), surveillance cultures, number of laboratory tests, culture exams, in addition to outcomes such as discharge, death, transfer and institution of exclusive palliative care. Reasons for admission were grouped using the International Classification of Diseases and Related Health Problems (ICD), such as respiratory, cardiovascular, renal, neurological, endocrine, digestive and other causes.[8]

The list of patients was obtained from reports from the hospital's pharmacy service, and the number of antibiotics dispensed was obtained from the electronic dispensing system. The cost of materials and medications as well as antimicrobial agents was extracted from the pharmacy service's electronic system, which calculates the mean of acquisition prices for the year, generating reports according to the patients' admission period.

Laboratory test results were also collected from the patient's electronic medical record. Surveillance cultures were for *Acinetobacter* sp. (skin swab), methicillin-resistant *Staphylococcus aureus* (MRSA) (nasal swab), vancomycin-resistant *Enterococcus* (VRE) (rectal swab) and carbapenemase (rectal swab). The methodology that the laboratory uses is culture in specific media and identification by MALDI-TOF/MS. For carbapenemase research, the laboratory also uses the "in house" phenotypic (colorimetric) test. For antimicrobial susceptibility testing, the laboratory uses BD Phoenix™ equipment or the Kirby Bauer technique. To define the minimum inhibitory concentration of polymyxin B, amikacin, imipenem and meropenem, the minimum inhibitory concentration technique by microdilution or E-test was used. Parameter analysis was performed by CLSI.

Statistical analysis

The variables observed quantitatively were described by mean, to indicate the central tendency, and by standard deviation (SD), to describe variability. Qualitative variables were described by counts and percentages.

Data normality was tested using the Kolmogorov-Smirnov test, and homogeneity of variances using Levene's test. Tests for differences between distributions were performed using the Kruskall-Wallis or Mann-Whitney U test, when it was not possible to assume variable normality. Association tests were performed using the chi-square test. Correlations of quantitative variables were observed using Pearson correlation analysis. Significance was established at $\alpha=0.05$, and the tests' significance estimate was calculated by two-tailed p-value<0.05.

The study was approved by the *Universidade Federal do Rio Grande do Sul* Research Ethics Committee, under Certificate of Presentation for Ethical Consideration (CAAE - *Certificado de Apresentação para Apreciação Ética*) 36216820.1.0000.5327 and favorable opinion 4.235.870 of August 25, 2020. The Data Use Commitment Form and the institution's Consent and Co-participation Form were signed. The research was conducted in accordance with the required ethical standards (Resolutions 466/2012, 510/2016 and 580/2018 of the Ministry of Health).

RESULTS

In total, data from 211 patients were included in the study. The mean age was 64.75 years (SD=15.89 years), 66.88 years for females (SD=16.02 years) and 62.57 years for males (SD=15.53 years old). The length of hospital stay was 15.29 days on average (SD=12.57 days), while the length of stay in the ICU was 9.69 days (SD=8.59 days). It is noteworthy that 64 (30.33%) patients had palliative care institutions during their admission, four of these (6.25%) were discharged and 60 (93.75%) died. The four palliative care cases that were discharged were allocated to the discharge outcome. Table 1 presents descriptive analysis of the sample.

Table 1. Demographic and clinical characterization of patients.

Patients (n=211)	N (%)
Sex	
Female	107 (50.71)
Male	104 (49.29)
City of origin	
Region Metropolitan	96 (45.49)
Porto Alegre	83 (39.34)
Outros	32 (15.17)
Comorbidities	
Hypertension	104 (49.28)
Diabetes mellitus	71 (33.64)
Chronic obstructive pulmonary disease	60 (28.43)
Chronic kidney disease	29 (13.74)
Stroke	23 (10.90)
Asthma	16 (7.58)
HIV[a] virus infection	13 (6.16)
Previous/active tuberculosis	11 (5.21)
Number of comorbidities (mean of 1.55/patient)	
None	37 (17.54)
1	72 (34.12)
2	61 (28.91)
3	34 (16.11)
>3	7 (3.32)
BMI[b]	
Underweight (BMI <18.5)	14 (6.64)
Normal weight (BMI ≥18.5 and <25.0)	73 (34.60)
Overweight (BMI ≥25 and <30)	67 (31.75)
Obesity (BMI ≥ 30)	57 (27.01)
Reasons for admission	
Respiratory	116 (54.98)
Cardiovascular	23 (10.90)
Renal	11 (5.21)
Neurological	9 (4.27)
Endocrine	7 (3.32)
Digestive	6 (2.84)
Others[c]	39 (18.48)
Outcomes	
Discharge	83 (39.34)
Palliative care – death	60 (28.44)
Death	57 (27.01)
Transfer	11 (5.21)

Laboratory tests-biological samples	
Blood	566 (54.48)
Tracheal aspirate/sputum	247 (23.77)
Urine	88 (8.47)
ABA[d] research in tracheal aspirate	49 (4.72)
VDRL[e]	39 (3.75)
Liquor	11 (1.06)
Others	39 (3.75)
Isolated strains species/genus	
Klebsiella pneumoniae	26 (13.98)
Staphylococcus aureus	25 (13.44)
Acinetobacter baumannii	22 (11.83)
Staphylococcus epidermidis	22 (11.83)
Pseudomonas aeruginosa	17 (9.14)
Escherichia coli	10 (5.37)
Others	64 (34.41)

Caption: *[a]Human Immunodeficiency Virus; [b]Body Mass Index; [c]Injuries, poisoning and some other consequences of external causes, musculoskeletal system and connective tissue diseases, skin and subcutaneous tissue diseases, infectious and parasitic diseases; [d]Acid-fast bacilli; [e]Venereal Disease Research Laboratory; diagnosis of syphilis.*

Table 2. Resistance profile of microorganisms – excluding duplicates.*

Bacteria	N	Total
Gram-negative		
Carbapenem-resistant *A. baumannii*	20	22
Polymyxin B-resistant *A. baumannii*	3	22
3rd generation cephalosporin-resistant *E. coli*	2	9
Carbapenem-resistant *E. coli*	0	9
3rd generation cephalosporin-resistant *K. pneumoniae*	12	22
Carbapenem-resistant *K. pneumoniae*	8	22
3rd-generation cephalosporin-resistant *Enterobacteriaceae*	0	25
Carbapenem-resistant *Enterobacteriaceae*	1	25
Carbapenem-resistant *P. aeruginosa*	0	14
Gram-positive		
MRSA[a]	3	21
Oxacillin-resistant CNS	9	13

**Duplicates: bacteria isolated from the same person, period less than 30 days; amethicillin-resistant Staphylococcus aureus.*

Of the total of 566 blood cultures, 73 (12.90%) showed growth of microbiota suggestive of contamination and 62 (10.95%) were positive, with 72 microorganisms isolated. Of these microorganisms, 36 (50%) were gram-positive, 29 (40.28%) were gram-negative, and seven were fungi (9.72%). Of the 247 tracheal aspirate/sputum collections, 25 (10.12%) showed growth of oropharyngeal microbiota and 61 (24.70%) were positive, isolating 67 microorganisms: 20 (29.85%) isolated bacteria were gram-positive; 47 (70.15%) were gram-negative. A total of 88 urine cultures were collected: 31 (35.23%) were positive, isolating 33 microorganisms, of which five (15.15%) were gram-positive, 17 (51.52%), gram-negative, and 11 (33, 33%), yeast. Table 2 shows resistance profile of isolated microorganisms.

The most prescribed class of antibiotics was cephalosporin, followed by penicillin and macrolide, as shown in table 3. Thus, 503 antibiotics were prescribed, resulting in a mean of 2.39 (SD=1.40) per patient. Furthermore, 79.52% were administered parenterally.

Table 4 shows the mean costs of admission and antimicrobial agents administered, stratified by category of reason for admission.

In Pearson correlation analysis, it was possible to identify a moderate correlation between the number of bacteria isolated from patients and length of stay in the ICU and total admission (ρ=0.540 and ρ=0.418, respectively). A low correlation was observed between total length of stay and quantity of bacteria identified in blood culture (ρ=0.305), tracheal aspirate (ρ=0.380) and urine culture (ρ=0.253). For analysis of length of stay in the ICU and bacteria identified in blood culture (ρ=0.249) and urine culture (ρ=0.248), correlations were low, whereas for tracheal aspirate (ρ=0.578), they can be considered moderate. It was not possible to identify significant associations between the number of bacteria isolated and outcomes.

A significant difference was identified between admission costs (p-value <0.008), antimicrobial costs (p-value <0.001) and percentage of costs related to antimicrobial

Table 3. Antibiotic prescription pattern by class - N (%).

Reasons for admission Antibiotic	Respiratory	Renal	Digestive	Endocrine	Neurological	Cardiovascular	Neurological	Others	Total
Cephalosporin	99 (67.81)	9 (6.17)	0 (0)	5 (3.42)	5 (3.42)	9 (6.17)	5 (3.42)	19 (13.01)	**146**
Penicillin	74 (56.92)	8 (6.15)	5 (3.85)	4 (3.08)	6 (4.61)	14 (10.77)	6 (4.61)	19 (14.62)	**130**
Macrolide	66 (81.48)	0 (0)	1 (1.23)	2 (2.47)	1 (1.23)	6 (7.41)	1 (1.23)	5 (6.18)	**81**
Carbapenem	19 (45.24)	2 (4.76)	1 (2.38)	0 (0)	0 (0)	3 (7.14)	0 (0)	17 (40.48)	**42**
Glycopeptide	18 (42.86)	0 (0)	1 (2.38)	0 (0)	1 (2.38)	2 (4.76)	1 (2.38)	20 (47.62)	**42**
Polymyxin	8 (50.00)	1 (6.25)	0 (0)	0 (0)	0 (0)	1 (6.25)	0 (0)	6 (37.50)	**16**
Sulfonamide	7 (46.66)	0 (0)	0 (0)	0 (0)	1 (6.67)	1 (6.67)	1 (6.67)	6 (40.00)	**15**
Antimycobacterial	9 (81.82)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (18.18)	**11**
Lincosamide	3 (50.00)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (50.00)	**6**
Aminoglycoside	4 (100.00)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	**4**
Quinolone	2 (50.00)	0 (0)	0 (0)	0 (0)	0 (0)	1 (25.00)	0 (0)	1 (25.00)	**4**
Azole	0 (0)	1 (33.33)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (66.67)	**3**
Nitrofuran	1 (50.00)	0 (0)	0 (0)	0 (0)	0 (0)	1 (50.00)	0 (0)	0 (0)	**2**
Oxazolidinone	1 (100.00)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	**1**
Total	**311**	**21**	**8**	**11**	**14**	**38**	**14**	**100**	**503**

Table 4. Costs with materials and medications due to admission

Reasons for admission	Admission cost (materials + medications)* (R$) Mean (SD)	Direct cost of antimicrobial agents (R$) Mean (SD)	Costs related to antimicrobial agents (%) Mean (SD)
Respiratory	2,786.97 (2,411.14)	297.95 (353.67)	13.10 (9.42)
Renal	1,164.91 (645.49)	132.63 (93.75)	11.04 (5.08)
Digestive	2,411.40(1,991.95)	132.04(110.83)	9.32 (10.61)
Endocrine	2,026.17 (2,441.31)	148.98 (87.17)	21.24 (23.31)
Neurological	2,229.17 (1,579.13)	176.24 (246.00)	7.70 (5.20)
Cardiovascular	1,394.47 (1,298.11)	196.50 (344.42)	12.34 (8.63)
Others	3,198.70 (5,589.20)	582.70 (1.405.97)	20.19 (12.58)

**Admission cost (materials + medications) corresponds to the total expenditure on materials and medications dispensed by the pharmacy, such as electrodes, bacteriological filter, surgical gloves, catheters, trichotomy device, extension for aspiration, extension for oxygen, sample collection bottle, syringes, probes, dressings, catheters, serums, equipment, masks, all medications available in the institution's therapeutic arsenal; SD: standard deviation.*

agents administered (p-value <0.001). For admission costs, only the distribution of cardiovascular diseases differs from respiratory diseases (p-value <0.017). For antimicrobial costs, the distribution of cardiovascular diseases differs from respiratory diseases (p-value <0.011) and other reasons for admission (p-value <0.002). While the distribution of the percentage of costs related to antimicrobial agents administered for other reasons for admission differs from respiratory (p-value<0.012) and neurological (p-value<0.012) diseases, for all other pairs, it was not possible to identify a significant difference.

As for surveillance cultures, considering the 211 patients included in the study, 844 samples should have been collected, four per patient. However, only 740 were collected. Of these samples, 718 were negative for the microorganisms studied and 22 were positive: 1 (4.55%) acinetobacter (skin swab); 6 (27.27%) MRSA (nasal swab); 13 (59.09%) carbapenemase-producing *Enterobacteriaceae* (rectal swab); and 2 (9.09%) VRE (rectal swab). Of the 20 patients who isolated microorganisms in surveillance swabs, only eight had culture tests showing growth, with 15 bacteria being isolated, ten of which had the same resistance characteristic as the microorganism isolated in the surveillance culture. For patients with positive surveillance cultures, the mean cost of antibiotics was R$213.84 (US$38.88) (SD=R$ 197.45 (US$35.90)). For those with negative surveillance cultures, the mean cost of antibiotics was R$ 339.15 (US$61.66) (SD=R$ 750.19 (US$136.39)). When considering the total costs of materials and medications, the positive ones had a mean of R$ 1,478.76 (US$268.86) (SD=R$ 1,204.07 (US$218.92)), and the negative ones, R$ 2,747.52 (US$499.54) (SD=R$ 3,250.10 (US$590.92)). Regarding the percentage of costs related to antibiotics, patients with isolated microorganisms had a percentage of 18.29% (SD=14.77%) of costs. The negative ones obtained a percentage of 13.40% (SD=10.05%) of costs. Patients with negative surveillance cultures used a mean of 2.1 antibiotics (SD=1.3 antibiotics). Those with positive surveillance cultures used a mean of 2.5 antibiotics (SD=1.4 antibiotics).

The outcomes were also observed for these 20 patients identified as colonized by some resistant bacteria. It was not possible to identify a significant association using the chi-square test (p-value>0.396). In these cases, 25% were discharged; 40% died; no patients were transferred; and in 35% palliative care was instituted.

DISCUSSION

Patients admitted to the ICU can have a very different profile and admission characteristics. Moreover, they may present infections during their stay in the unit due to several factors.

In the study, of the 211 patients, 17.5% did not present any comorbidity, unlike a study carried out in 1,265 centers in 75 countries, whose value was 48.5%.[10] When comparing the reasons for admission, the data were similar to those in the literature, such as respiratory causes (54.98%), followed by cardiovascular causes (10.90).[10] Mean length of stay in the ICU (9.69 days) and admission (15.29 days) were similar to those found in a German study, with an average of 14 days of admission,[11] however different from a study in Romania, with an ICU stay of 6.9 days.[3] The high mortality rate found (55.45%) surpassed studies with similar designs and ICU characteristics.[3,10] These differences can be considered by excluding post-operative patients in our study, since they have a shorter hospital stay, fewer complications, a more favorable outcome and, therefore, a shorter hospital stay.

In ICUs, antibiotics are commonly administered via parenteral routes, which was observed in our results (79.52%) and in a study carried out in five ICUs, where 98.7% were administered via this route.[1] The use of azithromycin exclusively orally, in tablet form, may justify this lower rate in the study results. The list of medications available for prescription in the hospital and the form of administration established by protocols can influence the profile of antimicrobial use, limiting the classes used.

The isolated microorganisms were predominantly gram-negative, coinciding with other studies in the literature in Brazilian ICUs[12,13] and studies with data from 83 countries.[8] *K. pneumoniae*, *S. aureus, A. baumannii, S. epidermidis* and *P. aeruginosa* were the most frequently

found microorganisms.[3,6] ICUs are favorable environments for the spread of microorganisms. In this regard, gram-negative microorganisms cause greater concern, as they present high rates of resistance and have fewer therapeutic options available in these cases.[13]

The results of this study showed that 90.91% of *A. baumannii* isolates were carbapenem-resistant, a profile similar to that found in two Brazilian ICUs (100% and 83.3%).[14] Regarding the prevalence of *Escherichia coli*, the result was similar to that found in the review of data from the Region of the Americas - 16% to 22%.[15] No samples of carbapenem-resistant *E. coli* were found, in agreement with data from other Brazilian ICUs, which were also not found.[14] The results for 3rd generation cephalosporin-resistant *K. pneumoniae* (54.54%) support those reported for the Region of the Americas[8] and Brazilian ICUs.[14] However, a significantly higher number of carbapenem-resistant *K. pneumoniae* was reported (36.36%) compared to 7.9% and 5.1% found in other Brazilian ICUs,[14] and 9% to 11%, found in the Region of the Americas.[15] For MRSA, the study result was 14.29%, different from other Brazilian ICUs, where 80% were reported,[14] and from a review study, which identified 42% to 55% of resistance.[15]

The most prescribed classes of antimicrobial agents were cephalosporin, penicillin and macrolide. Meanwhile, in a study including 1,150 centers in 88 countries, the classes were penicillin, carbapenem and cephalosporin.[8] A lower prevalence of carbapenem prescription was found when compared to global data,[8] which may indicate a preservation of this broad-spectrum antibiotic in the study ICU. The different epidemiological and clinical profiles and protocols of each institution may also justify the differences in the prescription pattern.

The moderate correlation between length of stay and quantity of bacteria can be explained by the length of treatment with antimicrobial agents necessary to complete the treatment of the infection. A study to assess the request for blood cultures demonstrated that there was no change in antimicrobial agent consumption with the reduction in the request for blood cultures.[16] The study hypothesis that patients without request for cultures would use antibiotics for longer was not empirically observed, demonstrating that treatment duration with antimicrobial agents tends to be longer when there are positive cultures.[16] When cultures were negative due to the absence of infection, the shorter length of stay can be explained because patients who do not have infection in intensive care do better,[10] being discharged earlier.

The moderate correlation between tracheal aspirate and the number of bacteria can be explained by the profile of microorganisms isolated in these samples, predominantly gram-negative. Although the majority of gram-negative urine cultures were also observed in urine cultures, positive urine cultures in asymptomatic patients are considered asymptomatic bacteriuria and treatment is not necessary.[17] Gram-negative bacteria found in tracheal aspirates are microorganisms closely related to pneumonia associated with mechanical ventilation,[18] which have high rates of multidrug resistance and fewer therapeutic options,[19] in addition to being associated with worse outcomes,[18] which may justify this increase in length of admission. In a study carried out in an Istanbul hospital, with follow-up for four years, a predominance of gram-negative microorganisms in tracheal aspirate was observed.[18]

The financial resources spent on antibiotics corresponded, on average, to 14.15% of direct costs of medications and materials. The results showed a lower cost of antibiotics in cardiovascular admissions, in line with the results highlighted by the Greek study.[9]

Among the 211 patients observed, 20 (9.48%) had positive results for surveillance cultures, and, for the institution's epidemiological profile, it is necessary to reflect on whether surveillance culture collection is really useful, since the collection criteria end up covering practically all patients admitted to the ICU. In order to rationalize the institution's resources, possibly carrying out only carbapenemase research, which was the surveillance culture with the highest positive rate, would be sufficient.

A study on the use of antibiotics in palliative care in ICUs stated that there is a vicious circle that involves the following order: length of stay; increased infection rate; use of antibiotics; infection by resistant microorganisms; use of broad-spectrum antibiotics; and longer hospital stay. Therefore, the use of antibiotics for patients in palliative care is contrary to the philosophy of palliative care itself, and is contraindicated.[20] In our study, palliative care was instituted in 30.33% of patients at the beginning or during ICU admission. Palliative care is still a new approach and requires more research to promote greater comfort and avoid the use of antibiotics unnecessarily.[20]

This work has the limitations inherent to single-center, cross-sectional observational studies. Furthermore, the specific characteristics of this ICU, with its epidemiological profile, the teams of prescribers and the list of medications available do not allow generalizing the results; furthermore, they provide understanding and encourage reflection on adopted procedures. Cost data should also be considered with caution, as it only considers data on direct costs with antimicrobial agents and total costs with materials and medications.

This study provides information that may assist in the development of institutional policies aimed at the rational use of antimicrobial medications and laboratory tests.

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AUTHORS' CONTRIBUTIONS

Lucia Collares Meirelles contributed to abstract conception, bibliographical research, writing, introduction, methodology, discussion, interpretation and description of results, preparation of tables, conclusions and final review of research. **Vera Lúcia Milani Martins** contributed to methodology, discussion, interpretation and description of results, preparation of tables, statistics and final review of research. **Diogo Pilger** contributed to research conception, methodology, discussion, interpretation of results, conclusions and final review.

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REVIEW ARTICLE

Patient safety climate in Primary Health Care in Brazil: an integrative review

Clima de Segurança do Paciente na Atenção Primária à Saúde no Brasil: revisão integrativa

Clima de seguridad del paciente en la Atención Primaria de Salud en Brasil: una revisión integradora

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Corresponding Author:
Herica Silva Dutra
herica.dutra@ufjf.br

Address: Rua José Lourenço Kelmer, s/n – Bairro São Pedro – Juiz de Fora, MG

Larissa Brandão Monte Mor[1];
Beatriz Francisco Farah[1];
Izabela Palitot da Silva[1];
Camila Ribeiro Araujo[1];
André Luiz Silva Alvim[1];
Luciane Ribeiro de Faria[1];
Herica Silva Dutra[1];

[1] *Universidade Federal de Juiz de Fora, MG, Brazil.*

ABSTRACT

Justification and Objectives: although Primary Health Care plays a central role in Brazil, much of the research that assesses safety culture and climate focuses on hospitals and few studies on this subject have explored this reality, thus justifying this study. The aim was therefore to identify the patient safety climate characteristics in Primary Health Care services in Brazil. **Methods:** an integrative review study. The MEDLINE via PubMed, LILACS, CINAHL and SciELO databases were used to search for studies. **Results:** nine articles were selected which reported on the negative safety climate in Primary Health Care. The five classes generated in the dendrogram are divided into two main categories: (1) Safe healthcare in Primary Health Care; and (2) Patient safety climate assessment in Primary Health Care services. Communication, organizational learning and teamwork were cited as enhancers of safe healthcare. Community health workers had a more negative safety climate perception. Working conditions and management support were rated negatively. **Conclusion:** strengthening the safety climate in Primary Health Care services favors quality of care and safe healthcare.

Keywords: *Patient Safety. Organizational Culture. Primary Health Care. Brazil.*

RESUMO

Justificativa e Objetivos: embora a Atenção Primária à Saúde tenha papel central no contexto brasileiro, grande parte das pesquisas que avaliam a cultura e o clima de segurança tem enfoque no âmbito hospitalar e poucas investigações sobre essa temática exploram essa realidade, justificando a elaboração deste estudo. Dessa forma, objetivou-se identificar as características do clima de segurança do paciente em serviços de Atenção Primária à Saúde no Brasil. **Métodos:** estudo de revisão integrativa. As bases de dados MEDLINE via PubMed, LILACS, CINAHL e SciELO foram utilizadas para busca das publicações. **Resultados:** foram selecionados nove artigos, que relataram sobre o clima de segurança negativo na Atenção Primária à Saúde. As cinco classes geradas no dendrograma se dividem em duas categorias principais: (1) Cuidado à saúde seguro na Atenção Primária à Saúde; e (2) Avaliação do clima

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de segurança do paciente nos serviços de Atenção Primária à Saúde. Comunicação, aprendizagem organizacional e trabalho em equipe foram citados como potencializadores do cuidado à saúde seguro. Os Agentes Comunitários de Saúde apresentaram percepção mais negativa do clima de segurança. As condições de trabalho e o suporte da gerência foram avaliados negativamente. **Conclusão**: o fortalecimento do clima de segurança nos serviços primários de saúde favorece a qualidade da assistência e o cuidado à saúde seguro.

Descritores: *Segurança do Paciente. Cultura Organizacional. Atenção Primária à Saúde. Brasil.*

RESUMEN

Justificación y Objetivos: a pesar de que la Atención Primaria de Salud desempeña un papel central en Brasil, gran parte de las investigaciones que evalúan la cultura y el clima de seguridad se centran en los hospitales y pocos estudios sobre este tema han explorado esta realidad, lo que justifica el desarrollo de este estudio. Por lo tanto, el objetivo fue identificar las características del clima de seguridad del paciente en los servicios de Atención Primaria de Salud en Brasil. **Métodos:** estudio de revisión integradora. Se utilizaron las bases de datos MEDLINE vía PubMed, LILACS, CINAHL y SciELO para la búsqueda de publicaciones. **Resultados:** fueron seleccionados nueve artículos que informaban sobre el clima de seguridad negativo en los servicios de Atención Primaria de Salud. Las cinco clases generadas en el dendrograma se dividen en dos categorías principales: (1) Atención de salud segura en la Atención Primaria de Salud; y (2) Evaluación del clima de seguridad del paciente en los servicios de Atención Primaria de Salud. La comunicación, el aprendizaje organizativo y el trabajo en equipo se citaron como potenciadores de una asistencia sanitaria segura. Los trabajadores sanitarios comunitarios tenían una percepción más negativa del clima de seguridad. Las condiciones de trabajo y el apoyo de la dirección se valoraron negativamente. **Conclusión:** reforzar el clima de seguridad en la Atención Primaria de Salud favorece la calidad de la atención y la seguridad de la asistencia sanitaria.

Palabra Clave: *Seguridad del Paciente. Cultura Organizacional. Atención Primaria de Salud. Brasil.*

INTRODUCTION

Adverse events related to healthcare are one of the main causes of deaths worldwide. However, it is known that many are avoidable situations through the implementation of strategies aimed at risk control and damage reduction.[1] This topic gained prominence following the publication of the document To Err is Human: Building a Safer Health Care System, which highlighted high rates of adverse events related to healthcare.[2,3]

In this sense, priority areas of action for patient safety were established, namely: correctly identifying patients; improve communication between healthcare professionals; improve safety in the administration of high-alert medications; ensure greater safety in surgical procedures; reduce the risk of healthcare-associated infections; and reduce the risk of pressure injuries and injuries resulting from falls.[4] In Brazil, actions aimed at patient safety intensified following the publication of specific regulations and the creation of the Brazilian National Patient Safety Program, aiming at qualified healthcare based on actions aimed at promoting a safety culture.[5]

To develop strategies to improve the safety of care provided, it is important that there is a positive safety culture in healthcare services.[6] Safety culture is characterized as a practice in which all workers, including managers and direct patient care workers, are responsible for their own safety, the safety of their colleagues, patients and family members; safety is a priority beyond financial and operational interests; identification, communication and resolution of safety-related problems are valued; the occurrence of accidents is the basis for organizational learning; maintaining safe health systems is achieved through the provision of resources, structure and accountability of all involved.[7]

Safety climate is the measurable portion of this safety culture, and can be assessed through the perceptions, behaviors and attitudes of individuals at a given time in the environment in which they are inserted.[8] The safety climate assessment of health services is capable of highlighting gaps and needs to improve the care provided by strengthening patient safety.[8-11]

It is worth noting that Primary Health Care (PHC) represents a model of change and reorganization of healthcare in Brazil,[12] based on disease prevention and health promotion.[12,13] There is a perception that PHC is relatively safe due to the low technological density used in this sector. However, the occurrence of incidents related to healthcare in primary care services is common,[14-17] which justifies the preparation of this study. It is worth noting that the Brazilian National Primary Care Policy (PNAB) and the Brazilian National Patient Safety Program highlight the need and importance of implementing patient safety actions within the scope of PHC.[16]

Therefore, this study aimed to identify the characteristics of patient safety climate in PHC services in Brazil.

METHODS

This is an integrative literature review carried out between May and October 2021. The integrative review was chosen because it is a method that enables the synthesis and analysis of published evidence on a topic, encompassing studies from different methodologies and contributing to in-depth regarding the topic studied.[18]

To carry out the present study, a systematization consisting of procedures organized into five chunks was

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followed: 1) conceptual; 2) methodological; 3) inferential; 4) theoretical; and 5) presentation. The first stage, constituted by the conceptual part of the review, encompasses topic identification and question elaboration. With regard to methodology, the steps of study survey and selection and data collection were followed. The inferential chunk comprises study assessment and data analysis, whereas the theoretical chunk brings the interpretation of findings and discussion of results. Finally, a presentation is made through a review synthesis.[19]

To prepare the research question, the PICo strategy for qualitative studies was used, being applied as follows: Population or Problem (PHC); Interest (Safety climate); Context (Brazil). In this way, the guiding question was defined: what are the characteristics of patient safety climate in PHC services in Brazil?

The search was carried out in the Medical Literature Analysis and Retrieval System Online (MEDLINE), Scientific Electronic Library Online (SciELO), *Literatura Latino-Americana e do Caribe em Ciências da Saúde* (LILACS) and Cumulative Index to Nursing and Allied Health Literature (CINAHL) databases. The following terms were defined to search the literature: patient safety, organizational culture, safety culture, safety climate, PHC, basic care, primary care and Brazil. The terms were associated with Boolean operators (AND and OR). The strategy employed was: "*Segurança do Paciente*" OR "Patient Safety" OR "*Seguridad del Paciente*" AND "*cultura de segurança*" OR "safety culture" OR "*cultura de seguridad*" OR "*clima de segurança*" OR "safety climate" OR "*clima de seguridad*" OR "*cultura organizacional*" OR "organizational culture" OR "*cultura organizacional*" AND "*atenção primária a saúde*" OR "primary healthcare" OR "*atención primaria de salud*" OR "*atenção básica*" OR "*atención básica*" OR "*cuidados primários*" OR "primary care") AND ("*Brasil*" OR "Brazil).

Inclusion criteria include articles available in electronic format, in full, in Portuguese, English and Spanish, with publication date from November 25, 2011. The temporal limitation is justified by the publication date of the regulation that guided regarding the good operating practice requirements for health services.[5] Exclusion criteria included articles that were unrelated to the study objective, research carried out in other countries, duplicate publications, articles that did not use an instrument that assesses safety climate, review articles, experience reports and research that was published in journals who did not have the peer review process.

To facilitate study selection, the Rayyan tool, website and bibliographic reference management application, was used.[20] Database searches were saved and exported to the Rayyan tool.

Data processing was carried out with the support of *Interface de R pour les Analyzes Multidimensionnelles de Textes et de Questionnaires* (IRAMUTEQ), which allows statistical analysis of texts using graphical representations, facilitating the organization and understanding of the materials studied.[21] The text *corpus* was constructed from the nine selected articles, including introduction, results and conclusion, adapting them to software specifications. The file was reviewed and typographical errors were corrected. Thus, the text *corpus* was processed in IRAMUTEQ, and the dendrogram generated by the program was adopted for data analysis.

The articles' level of evidence was assessed according to Agency of Healthcare Research and Quality (AHRQ) recommendations.[22] For data analysis, we opted for the content analysis modality.[23] Content analysis is structured into three phases. In the first phase, also called pre-analysis, the material is read briefly, the documents that will be analyzed are selected, the objectives are formulated and the material is prepared. Material exploration is the second phase of analysis and is characterized by material coding and categorization. The last phase is treatment of results, where interpretation of results is carried out through inference.

RESULTS

An adapted version of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol flowchart was used to expose the steps of the search process (Figure 1).

After identifying and excluding duplicate studies, study titles and abstracts were read, excluding those that did not meet the inclusion and exclusion criteria and pre-selecting those that met these criteria. Subsequently, the 11 pre-selected articles were read in full and two of them were excluded, one because it was a master's thesis and the other because it did not use an instrument to assess safety climate. Finally, nine articles were selected to compose the study sample.

Selected studies were grouped in Chart 1 and characterized according to main author, journal title and year of publication, article title, research location and sample, data collection instrument used and synthesis of the main results obtained. Of the nine articles selected, eight were published in Portuguese and one in English. The year of publication ranged from 2013 to 2021. The number of research participants ranged from 51 to 513, with an average of 198 participants.

The instruments used to assess patient safety climate varied between articles. Among them, two used the translated and culturally adapted version of the Safety Attitudes Questionnaire (SAQ), and five chose the translated and culturally adapted version of the Medical Office Survey on Patient Safety.[32,33] The SAQ-AV was adopted in two articles.[34]

It is worth mentioning that the first study[24] included in the review that used the SAQ-AV informs the authors' authorization to translate, adapt and apply the instrument in Basic Health Units. However, evidence of validity of that instrument in the Brazilian context was not presented. The second study[26] included in the review that uses the SAQ-AV makes reference to the previously mentioned study[24]. Despite this observation, it is noteworthy that the studies were published in journals indexed in reputable health databases, with a rigorous peer review process. Therefore, it was decided to keep them in the

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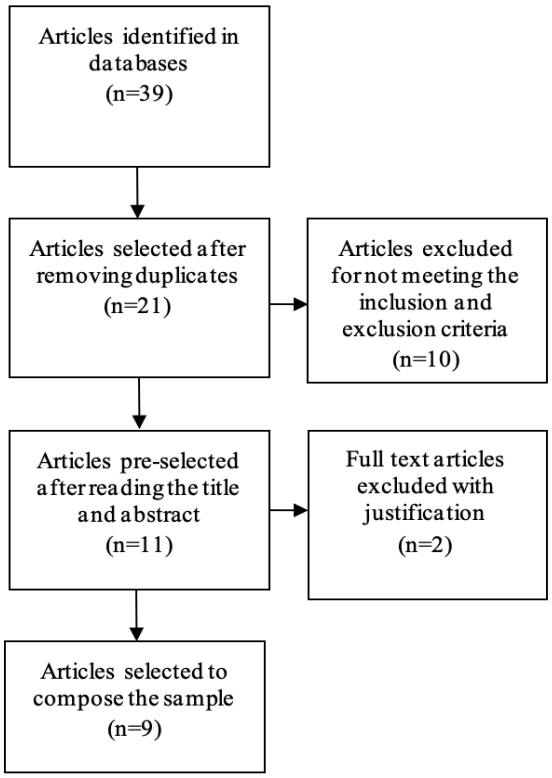

Figure 1. Flowchart of the search process according to the PRISMA protocol. Juiz de Fora, MG, Brazil, 2022.

sample selected for this investigation.

All articles included in this study had a cross-sectional design, being classified with a level of evidence equal to 6. It is noted that, despite using different terms and specifications, the instruments converge in the sense of assessing broader themes regarding safety climate, such as such as interpersonal relationships, covering communication and teamwork, the relationship with management and working conditions.

Among the studies assessed, the participating professional categories were nurses, doctors, community health workers (CHW), nursing technicians, dentists, social workers, psychologists, pharmacists, physiotherapists, speech therapists, managers, nutritionists, physical educators, occupational therapists, administrative assistants, nursing assistants, pharmacy assistants, oral health assistants, clinical pathology and laboratory service assistants and endemic disease agents.

In this study, we chose to use the Descending Hierarchical Classification (DHC), which allows the organization of words and the formation of classes based on the context relationship and association between words.[21] After grouping the words, a dendrogram was created showing the classes generated and the proportion of text segments that make up each class (Figure 2).

The *corpus* classification made it possible to identify two main categories, including three classes in category

Chart 1. Characterization of selected studies according to main author, journal, year, location, sample, data collection instruments used and main results. Juiz de Fora, MG, Brazil, 2022.

Author, journal/year	Location/ sample	Data collection instrument	Main results
Paese F, Dal Sasso GTM Texto Contexto Enferm/ 2013[24]	Santa Catarina (n=96)	Safety Attitudes Questionnaire Ambulatory Version	The "patient safety" attitude proved to be most relevant to study participants. The "error" attitude was assessed as the least relevant.
Galhardi NM et al. Acta Paul Enferm/ 2018[25]	São Paulo (n=240)	Survey on Patient Safety Culture for Primary Care	Professionals presented positive perceptions regarding the dimension of service quality and patient safety climate. The "leadership support" dimension proved to be fragile, requiring improvements.
Raimondi DC et al. Rev Gaúcha Enferm/2019[7]	Paraná (n=144)	Survey on Patient Safety Culture for Primary Care	The patient safety climate was assessed as positive by study participants.
Souza MM et al. Rev Bras Enferm/2019[26]	Rio Grande do Sul (n=349)	Safety Attitudes Questionnaire Ambulatory Version	Professionals' assessment of safety climate was negative. Only the "patient safety" domain presented a positive assessment. The domains that presented the lowest means were "working conditions" and "error".
Dal Pai S et al. Rev Baiana Enferm/ 2020[27]	Rio Grande do Sul (n=188)	Survey on Patient Safety Culture for Primary Care	The assessment of the professionals participating in the study in relation to safety climate was positive, except in the "pressure and pace of work" dimension.
Lousada LM et al. BMC Family Practice/ 2020[28]	Ceará (n=147)	Safety Attitudes Questionnaire	Patient safety climate was assessed negatively. "Job satisfaction" was the domain that obtained the best score, while "management perception" and "working conditions" were those with the lowest scores.
Macedo LL et al. Trab. Educ. Saúde/ 2020[29]	Paraná (n=513)	Survey on Patient Safety Culture for Primary Care	A negative patient safety climate assessment was identified. The most fragile dimensions according to the assessments were "work process in the health service" and "manager support".
Vasconcelos PF et al. Rev Min Enferm/ 2021[30]	Ceará (n=55)	Safety Attitudes Questionnaire	Patient safety climate in the studied scenario was negatively assessed. All domains assessed presented values lower than those recommended; among them, three showed the need for interventions to improve patient safety climate.
Bohrer JKL et al. Rev Rene/ 2021[31]	Federal District (n=51)	Survey on Patient Safety Culture for Primary Care	No strong dimensions of safety climate were identified. The "teamwork" dimension was the one that received the best assessment.

1 and two classes in category 2, namely: 1) Safe healthcare in PHC (class 1: Aspects of safe healthcare in PHC; class 2: Patient safety; and class 3: Patient safety culture in PHC); and 2) Patient safety climate assessment in PHC services (class 4: Perceptions about patient safety climate according to professional categories; and class 5: Patient safety climate assessment in PHC services). Thus, the thematic proximity between the classes allowed them to be addressed and discussed in an integrated way within each corresponding category.

In category 1, "Safe healthcare in PHC", the main aspects for safe healthcare in PHC were highlighted, with a view to improving patient safety culture. Communication and teamwork were highlighted as enhancers for safe care. Within this category, the relevance of organizational learning stood out as an element capable of promoting positive transformations in the work environment through the sharing of information and implementation of strategies in health services. Furthermore, the non-punitive culture is characterized by a differential in promoting patient safety.

In category 2, "Patient safety climate assessment in PHC services", PHC professionals' perception about patient safety climate is presented. It is worth highlighting the challenge faced in the present study related to the use of different assessment instruments. The Family Health Strategy (FHS) model was positively associated with patient safety climate and length of experience in PHC. Conversely, being a CHW, having deficiencies in management and leadership, in addition to inadequate working conditions, were related to an unfavorable safety climate perception. Safety climate in PHC was considered negative.

DISCUSSION

Patient safety climate characteristics in PHC services in Brazil point out aspects related to safe care for users as well as the factors identified in health workers' perception.

Communication continues to be a challenge in the context of PHC. Problems and failures in communication can harm the quality and safety of the care provided. Effective communication is necessary both between professionals and between professionals and users to prevent incidents and strengthen safe healthcare.[7,26,30,31]

Among the challenges for effective communication in the health work process, it is possible to mention: uniprofessional action; the traditional training process; and hierarchical issue, which sometimes prevents establishing fluid communication and sharing of information. For effective communication and quality of healthcare, it is necessary for professionals to know each other's responsibilities and understand the importance of teamwork. Therefore, investing in training can be an effective strategy to strengthen relationships between the team, encourage open communication and collaborate in the work process.[35,36]

Teamwork was positively assessed in some of the studies analyzed.[24,25,27] An integrated team is better able to develop its work process effectively, having common objectives and strategies to achieve safe assistance.[37,38] Teamwork is crucial for the comprehensiveness of care and the quality of assistance in PHC. Interprofessional collaborative practice is based on effective communication between the team, common objectives and collectively developed goals, and shared responsibility for quality of work.[35-38]

Organizational learning was an aspect considered important for care safety in PHC. The assessment of organizational learning varied in the studies that assessed this element. However, they understand that learning on the job through continuing education is essential for professional updating, promotion of dialogue and exchange of knowledge to build critical thinking for work focused on safe practices.[7,24-27,30,31]

Organizational learning is a broad concept that is still much discussed. It is understood as a strategy to transform knowledge into action and create knowledge that is shared among the health teams of an institution.[39] Continuing education provides significant learning based on the reality and demands of everyday service life, allowing workers to expand their autonomy and become leading actors in safe care for users and themselves, promoting changes in organizational culture.[40]

To strengthen patient safety, another point to be highlighted is learning from error to replace individual blame. In this regard, it is necessary to understand the error as a system failure and not an individual failure, leading professionals to be co-responsible for the incident that occurred and encouraging collective learning from the error.[4,7,16]

Working on the FHS team and having five to 12 years of work were significant factors for a positive safety culture.[26] FHS is based on comprehensive care, developed by a multidisciplinary team and aimed at the population in a defined territory. Professional performance in the FHS team can contribute to creating bonds with users and professional satisfaction.[12] Likewise, longer service time promotes greater job satisfaction, contributing to safe and quality care.[6]

Safety climate assessment between professional categories varied between studies. Three of the selected articles[7,24,29] indicated that there was a weaker safety climate perception among CHW. The dimensions negatively assessed by these professionals were linked to teamwork and communication, health unit management and working conditions. This finding can be justified by CHW's work being developed in the health unit, but mainly in the community in which it is located,[7] which can create a distance in relation to other team members.

Perception and support from management were one of the most negatively assessed aspects in studies.[7,24,25,28-30] Sometimes, the relationship with management is ineffective, which can harm teamwork and, consequently, patient safety. The role of coordinator in PHC requires tools such as leadership, a necessary aspect for improving work processes and changes in health services.[16] The fragility of interaction with management can influence attitudes related to patient safety. Thus, it is important that management is open to dialogue and supports the daily work of professionals, in order to promote communication about safety and jointly develop

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actions aimed at improving safety climate.[38]

Unfavorable working conditions can impact patient safety.[24,26-29] The factors cited by professionals are work overload, professional exhaustion, absence of a manager in the unit, scarce resources, lack of inputs and fragile work relationships. These factors influence the provision of services and the quality of care provided, in addition to contributing to professional dissatisfaction.[4]

Most studies[26,28-31] showed that the patient safety climate was assessed as negative. Knowing the safety climate in PHC is important to identify both the strengths and weaknesses of the service in relation to patient safety and, thus, seek strategies to improve the conditions assessed.[14,16] The results of the institutional assessment can support the development of an action plan to be worked on together with the team, management and users of health services.

Limitations of this study include limited databases and the inclusion of studies published in only three languages. The choice of databases and languages is justified due to the chosen scenario being Brazil. In this way, the databases and languages include the main vehicles of studies produced in the Brazilian context. Furthermore, the use of different instruments for measuring the patient safety climate in the selected studies did not allow the development of comparisons between studies. As a weakness, the level of evidence of studies included is highlighted. Methodological rigor and assessment of studies by independent reviewers were the strategies adopted to promote greater robustness to the study and mitigate the limitations highlighted. The lack of evidence of validity of SAQ-AV in studies that used this instrument may signal weakness in the results of both studies (Paese F, Dal Sasso GTM, 2013[24] and Souza MM, Ongaro JD, Lanes TC *et al*., 2019[26]), which may impact the conclusions of this review. In this regard, the importance of cross-cultural adaptation studies of foreign measuring instruments to adapt to the Brazilian context and research scenarios stands out.

In addition to the issues highlighted, it is worth highlighting that strategies are recommended to improve safety climate in PHC, such as: implementation of continuing education in health services with a focus on learning through error; holding periodic team meetings to improve interaction and promote discussions and exchange of knowledge; use of protocols and checklists; improvement of working conditions; and management support to improve the work process.[7,24-27,29,31]

CONCLUSION

Safety climate in PHC was negative in most of the studies analyzed. Communication, organizational learning and teamwork were cited as enhancing safe healthcare. Having five to 12 years of work and working on the FHS team were significant aspects of a positive safety culture. CHW presented a worse assessment of safety climate when compared to other PHC workers. Management support and working conditions were the dimensions that presented the worst assessments.

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AUTHORS' CONTRIBUTIONS

Larissa Brandão Monte Mor contributed to bibliographical research, writing the abstract, introduction, methodology, discussion, interpretation and description of results, preparation of tables, conclusions, review and statistics. **Beatriz Francisco Farah** contributed to writing the abstract, review and statistics. **Izabela Palitot da Silva** contributed to writing the abstract, review and statistics. **Camila Ribeiro Araujo** contributed to writing the abstract, review and statistics. **André Luiz Silva Alvim** contributed to writing the abstract, methodology, interpretation of results, conclusions, review and statistics. **Luciane Ribeiro de Faria** contributed to writing the abstract, review and statistics. **Herica Silva Dutra** contributed to project administration, literature research, abstract writing, introduction, methodology, discussion, interpretation and description of results, conclusions, review and statistics.

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Corresponding Author:
Raphaella Castro Jansen
raphaella.jansen@gmail.com

Address: R. George Rocha, 50 - Demócrito Rocha, Fortaleza - CE, 60520-100

Raphaella Castro Jansen[1];
Maria Rayssa do Nascimento Nogueira[2];
Vitória Talya dos Santos Sousa[3];
Vitória Costa Oliveira[1];
Anne Fayma Lopes Chaves[2];

[1] *Hospital e Maternidade Dra. Zilda Arns Neumann (HMDZAN), Fortaleza, CE, Brazil.*
[2] *Universidade da Integração Internacional da Lusofonia Afro-Brasileira (UNILAB), Redenção, CE, Brazil.*
[3] *Escola de Saúde Pública do Ceará (ESP), Fortaleza, CE, Brazil.*

ABSTRACT

Background and Objectives: investigating the relationship between breast milk use infection control in premature newborns may provide a basis for continuing exclusive breastfeeding, reducing the rates of early introduction of formula and strengthening their immune system. In view of this, the objective was to analyze the relationship between breastfeeding and infection control in premature newborns. **Content:** an integrative review, which included original articles, available electronically and with a temporal cut of the last five years. Searches were carried out in August 2022 in the Medical Literature Analysis and Retrieval System Online, *Literatura Latino-Americana e do Caribe em Ciências da Saúde*, Scopus, Web of Science and Science Direct databases, using the descriptors Breastfeeding, Milk Human, Infection Control, Infection Control and Premature Newborn, concatenated with the search operators "AND" and "OR". The Rayyan digital tool was used to organize the study selection stages. A total of 490 studies were identified in the search, of which seven were selected. All studies were published in English between 2018 and 2022. Regarding design, three were case-control studies, one was a cohort, one was cross-sectional, and two were clinical trials. Regarding the level of evidence, studies classified as level IV predominated. **Conclusion:** human breast milk has the power to reduce the incidence of necrotizing enterocolitis and cytomegalovirus, reduce the worsening of inflammatory states and late-onset sepsis, prevent diseases, encourage the physical and cognitive development of premature newborns.

Keywords: *Milk Human. Breast Feeding. Infection Control. Infant Premature.*

RESUMO

Justificativa e Objetivos: a investigação da relação do uso de leite materno com o controle de infecções em recém-nascidos prematuros poderá fornecer embasamento para continuidade do aleitamento materno exclusivo, diminuindo os índices de introdução precoce de fórmula e propiciando o fortalecimento de seu sistema imunológico. Diante disso, objetivou-se analisar a relação do aleitamento materno com o controle de infecções em recém-nascidos

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prematuros. **Conteúdo:** revisão integrativa, que incluiu artigos originais, disponíveis eletronicamente e com recorte temporal dos últimos cinco anos (2018 a 2022). Foram realizadas buscas no mês de agosto de 2022 nas bases de dados *Medical Literature Analysis and Retrieval System Online*, Literatura Latino-Americana e do Caribe em Ciências da Saúde, Scopus, *Web of Science* e *Science Direct*, sendo utilizado os descritores Aleitamento Materno, Leite Humano, Controle de Infecções, Controle de Infecção e Recém-Nascido Prematuro, concatenados com os operadores de pesquisa *"AND"* e *"OR"*. Foi utilizada a ferramenta digital Rayyan para a organização das etapas de seleção dos estudos. Foram identificados 490 estudos na busca, dos quais sete foram selecionados. Todos os estudos foram publicados em inglês entre 2018 e 2022. Quanto ao delineamento, três eram estudos de caso controle, um era coorte, um era transversal e dois eram ensaios clínicos. Em relação ao nível de evidência, predominaram os estudos classificados em nível IV. **Conclusão:** o leite humano materno tem o poder de diminuir a incidência de enterocolite necrosante e citomegalovírus, reduzir o agravamento de estados inflamatórios e de sepse tardia, prevenir doenças, estimular o desenvolvimento físico e cognitivo do recém-nascido prematuro.

Descritores: *Leite Humano. Aleitamento Materno. Controle de Infecções. Recém-Nascido Prematuro.*

RESUMEN

Justificación y Objetivos: investigar la relación entre el uso de la leche materna y el control de infecciones en los recién nacidos prematuros puede brindar una base para continuar con la lactancia materna exclusiva, reducir las tasas de introducción temprana de fórmula y fortalecer su sistema inmunológico. Ante ello, el objetivo fue analizar la relación entre la lactancia materna y el control de infecciones en recién nacidos prematuros. **Contenido:** revisión integradora, que incluyó artículos originales, disponibles electrónicamente y con un corte temporal de los últimos cinco años. Las búsquedas se realizaron en agosto de 2022 en las bases de datos *Medical Literature Analysis and Retrievel System Online*, *Literatura Latino-Americana e do Caribe em Ciências da Saúde*, *Web of Science* y *Science Direct*, utilizando los descriptores Lactancia Materna, Leche Humana, Control de Infecciones, Control de Infecciones y Recién Nacido Prematuro, concatenado con los operadores de búsqueda "AND" y "OR". Se utilizó la herramienta digital Rayyan para organizar las etapas de selección de estudios. En la búsqueda se identificaron 490 estudios, de los cuales se seleccionaron siete. Todos los estudios fueron publicados en inglés entre 2018 y 2022. En cuanto al diseño, tres fueron estudios de casos y controles, uno fue de cohorte, uno fue transversal y dos fueron ensayos clínicos. En cuanto al nivel de evidencia predominaron los estudios clasificados como nivel IV. **Conclusión:** la leche materna humana tiene el poder de reducir la incidencia de enterocolitis necrotizante y citomegalovirus, reducir el agravamiento de estados inflamatorios y sepsis tardía, prevenir enfermedades, estimular el desarrollo físico y cognitivo de los recién nacidos prematuros.

***Palabras Clave*:** *Leche Humana. Lactancia Materna. Control de Infecciones. Recién Nacido Prematuro.*

INTRODUCTION

The neonatal period is considered critical due to hemodynamic instability and the immature physiological characteristics of low birth weight and premature newborns (NB). Furthermore, the immune system of this population is still developing, making them more susceptible to infections.[1]

In addition to these factors, preterm and low birth weight newborns (PTNB) become more vulnerable to bacterial infections due to prolonged hospitalization, environmental exposures in the Neonatal Intensive Care Unit (NICU), need for invasive procedures and of treatments that compromise the defense mechanism.[2,3]

The inflammatory process resulting from these infections is related to the development of complications that can induce neonatal sepsis, bronchopulmonary dysplasia, intraventricular hemorrhages and necrotizing enterocolitis. All of these diseases are considered risk factors for neonatal mortality, as they affect various organs such as the lungs, brain and intestine. Furthermore, they lead to a high number of neonatal deaths.[4]

According to data collected by the United Nations Children's Fund, infections account for approximately 21% of NB deaths worldwide, being considered a public health problem.[5] In Brazil, infections are the third most prevalent cause of death among premature babies (18.5%).[6]

Therefore, it is essential to know the development of the microbiome, in addition to factors that can influence infection prevention, such as the type of food offered, especially human milk (HM).[7]

HM contains important properties for the development of NB, such as nutrients, a rich variety of vitamins, minerals, proteins, fats, carbohydrates, and a range of antibodies capable of protecting the immune system against pathological microorganisms.[8] In the context of preterm infants, exclusive breastfeeding (EBF) is considered a strong ally in reducing infections and, consequently, neonatal morbidity and mortality.[9,10]

Given that preterm infants face a greater risk of infections due to the immaturity of the immune system, identifying effective strategies to strengthen the immunity of these babies is essential to reduce morbidity and

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mortality associated with neonatal infections. Considering the molecular composition of HM and its action on the NB's immune system, investigating the relationship between breastfeeding and infection control is crucial to understanding how this practice can positively impact the health of these babies. Gathering and synthesizing data on this topic provides a collection of information that can help health professionals make informed decisions, promoting evidence-based clinical practice. This is particularly relevant for guiding health policy and neonatal care practices.

Given this context, the following question arose: what is the relationship between breastfeeding and infection control in PTNB? The investigation of this scenario may provide a basis for continuation of EBF for PTNBs, reducing the rates of early introduction of formula in the ICU, enabling the strengthening of the immune system of these NBs, which may increase their survival, acting directly on reducing morbidity and mortality rates for this population. Therefore, this study aimed to analyze the relationship between breastfeeding and infection control in PTNB.

METHODS

This is an integrative literature review, carried out in six stages: 1) theme and guiding question definition; 2) definition of inclusion and exclusion criteria; 3) study extraction; 4) analysis of selected studies; 5) interpretation of results; 6) data synthesis.[11] Moreover, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) was used to organize and present the results.[12]

The guiding research question was formulated, based on the PICo strategy, an acronym for Patient, Interest and Context.[13] Thus, PTNB was assigned to P, risks and benefits of breastfeeding to I and control and development of infections to Co. Therefore, the following question was elaborated: what is the relationship between breastfeeding and infection control in PTNBs? Therefore, this research included studies that dealt with the PTNB population, whose phenomenon of interest is the risks and benefits of breastfeeding in the context of infection control in prematurity.

Original articles that answer the guiding question, without language limits, available in full in open access journals and with a five-year time frame (2018 to 2022) were included. The temporal delimitation was made in an attempt to promote an ideal sample of original studies, given that a high sample of articles can make it difficult to conduct the integrative review, or cause biases in the stages.[14] Duplicate articles and those that did not respond to the research object were excluded.

As for data extraction, it began by collecting articles online, which took place in August 2022, through access to five databases, via the Academic Community Federated on the Coordination for the Improvement of Level Personnel Higher Education (CAPES - *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior*) Journals Portal, such as Medical Literature Analysis and Retrieval System Online (MEDLINE) (via PubMed), Latin American and Caribbean Literature in Health Sciences (LILACS) (via Virtual Health Library), Scopus, Web of Science and Science Direct.

To search for articles, we used the descriptors in Portuguese *Recém-Nascido Prematuro*, *"Aleitamento Materno"/"Leite Humano"*, "*Controle de Infecções*", extracted from the Health Sciences Descriptors (DeCS), and its synonyms in English, "Infant, Premature", "Breast Feeding"/"Milk, Human", "Infection Control", obtained through Medical Subject Headings (MeSH). The descriptors were crossed with the Boolean operators "AND" and "OR".

As a result, search strategies were used according to the specificities of each database: MEDLINE - Breast Feeding OR Milk, Human AND Infection Control AND Infant, Premature; LILACS - *Aleitamento Materno* OR *Leite Humano* AND *Controle de Infecções* OR *Controle de Infecção* AND *Recém-Nascido Prematuro*; Scopus - Breast Feeding OR Milk, Human AND Infection Control AND Infant, Premature; Web of Science - (((ALL=(BreastFeeding)) OR ALL=(Milk, Human)) AND ALL=(InfectionControl)) AND ALL=(Infant, Premature); and Science Direct - Breast Feeding AND Infection Control AND Infant, Premature.

Study searches and selection was carried out in August 2022 independently by two reviewers, nurses and students from an academic master's program. The studies found were exported to Rayyan Web for identification, exclusion of duplicates and decision to remain the studies by the blind authors.[15] Additional reference managers were not used, as the use of Rayyan was considered sufficient. Initially, the inclusion and exclusion criteria were analyzed, and the subject was screened, which included reading the title and abstract. Subsequently, eligible references were read in full. When differences of opinion were identified, a third reviewer was appointed to read and issue a conclusive opinion, with the aim of ensuring methodological rigor in the process of selecting and including studies.

The data extracted for the qualitative analysis of articles was based on an instrument previously prepared by the reviewers, adapted from the instrument constructed and validated in 2005 by Ursi and Gavão, which contains identification (authorship, title, place and year of publication), objective, methodological design, sample, main results, outcomes and level of scientific evidence variables.[16] Adaptation is justified by the non-relevance, for the present study, of some items from the original instrument. Descriptive synthesis of the data in this review is presented according to the use of image resources, illustrated through a table and figure, organized into categories with subsequent discussion in the light of specialized scientific literature.

The following classification of levels of evidence was used: level I – systematic review or meta-analysis; level II – randomized clinical trial; level III – non-randomized clinical trial; level IV – cohort study or case-control study; level V – study resulting from a systematic review, descriptive and qualitative study; level VI – study derived from a single descriptive or qualitative study; level VII – expert opinion.[17]

As this was a review study, submission to the Rese-

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arch Ethics Committee was not necessary. It is noteworthy that all ethical precepts were followed when carrying out the research.

RESULTS AND DISCUSSION

Initially, 490 studies were identified in the databases. In the first analysis, 26 articles were excluded due to duplication and 453 were removed for not answering the guiding question, after reading the titles and abstracts. In the second analysis, by reading the articles in full, four articles that did not answer the guiding question were excluded. Finally, seven articles made up the final sample (Figure 1).

Of the seven articles analyzed, all were published in English, with four (57.14%) developed in Europe and three (42.85%) in America. It can be suggested that the development of most research in Europe is an attempt by the academic and scientific community to raise awareness of people on the importance of breastfeeding, given the low rates of EBF on the continent.[18-24] In 2015, of the 21 countries in the region, only 13% of babies up to six months were exclusively breastfed with HM.[25]

It is worth highlighting, however, the lack of data collected in Brazilian territory. Despite not matching Europe in terms of low breastfeeding rates, the country still needs to improve its numbers. According to research by the Ministry of Health carried out between 2019 and 2020, among the 14,505 children under five years old assessed, 45.7% of those under six months old were on EBF.[26]

It was also found that three (42.85%) were case control studies, one (14.28%) was a cohort, one (14.28%) was cross-sectional and two (28.57%) were clinical trials - one was not randomized and one randomized.[18-24] Regarding the level of evidence, studies classified with level IV evidence predominated (n=4; 57.14%), characterized by cohort/case control studies (Chart 1). Despite the diversification of the methodological approaches gathered, it was observed that the majority of studies demonstrate the effectiveness of HM against infections.

The main results of the studies analyzed showed that breastfeeding is related to infection control in PTNB by promoting several benefits to PTNBs that reduce the risk of the onset of this condition. Subsequently, inn Chart 2, the benefits of offering HM in PTNB for infection control are presented, according to the articles analyzed.

When considering the findings that answer the guiding question of this work, it was observed that HM is related to infection control in PTNB by promoting several benefits to PTNB that reduce the risk of the appearance of this condition. This highlights the need to keep babies on HM, even when admitted to the NICU and given the difficulties presented for effective practice.[27]

Mothers, however, may experience distress due to the fear of not being able to breastfeed, which therefore requires support from the multidisciplinary team to help these mothers adhere to and maintain breastfeeding.[28] Thus, it is observed that it is necessary for health professionals working in ICUs to view HM not only as a food, but as an essential infection prevention measure for the development of the newborn and hospital discharge.

It was seen that the benefits of breastfeeding for controlling infections in preterm infants most cited in studies include a reduction in the incidence of late-onset sepsis (28.57%), necrotizing enterocolitis (42.85%) and the inflammatory state (28.57%).

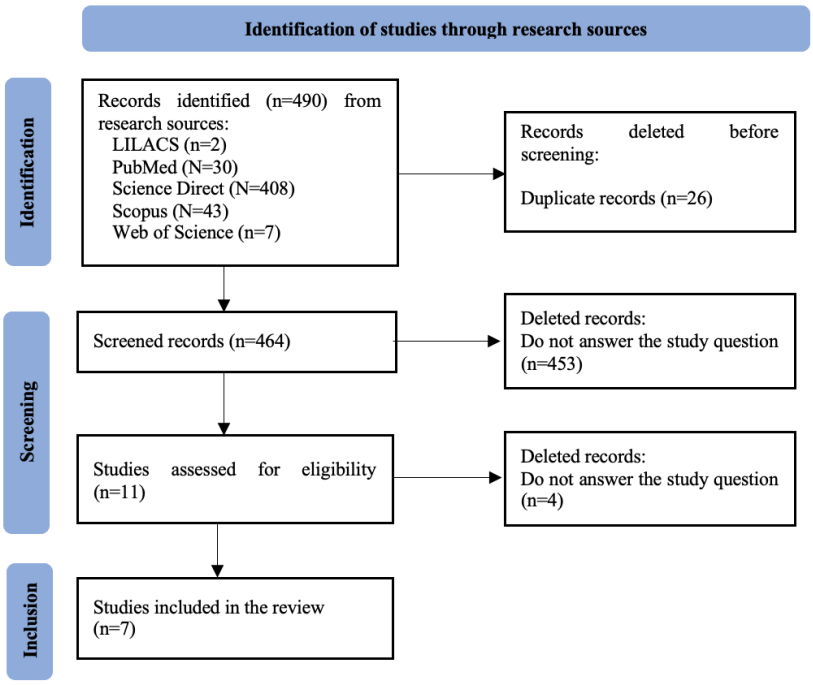

Figure 1. Flowchart for identification and selection of studies according to PRISMA, 2020

Chart 1. Synthesis of studies included in the final sample.

Code	Title	Authors and year	Location/ sample	Objective	Design/LoE*	Main results
A1	Oropharyngeal Colostrum Positively Modulates the Inflammatory Response in Preterm Neonates	Martín-Álvarez et al., 2020[18]	Spain/ 100 NB†	Assess the effects of oropharyngeal breast milk administration on the inflammatory response of extreme preterm infants.	Case-control/ Level IV	The administration of oropharyngeal breast milk contributes to reducing the pre-inflammatory state of preterm infants‡ and provides complete enteral nutrition earlier.
A2	Availability of Donor Human Milk Decreases the Incidence of Necrotizing Enterocolitis in VLBW Infants	Cohen et al., 2020[23]	USA/ 9,400 NB†	Determine whether a project to promote HM feeding would be associated with a decrease in necrotizing enterocolitis.	Cross-sectional/ Level V	The incidence of necrotizing enterocolitis was reduced by 40% with the availability and supply of HM to NB.
A3	Team-Based Implementation of an Exclusive Human Milk Diet	Manthe et al., 201922	USA/ 225 NB†	Describe the teamwork, steps taken, and systems created to protect, implement, and maintain an all-HM diet.	Case-control/ Level IV	Administration of an exclusive HM diet significantly reduced the occurrence of late-onset sepsis, bronchopulmonary dysplasia, necrotizing enterocolitis and favored weight gain.
A4	Short-term Pasteurization of Breast Milk to Prevent Postnatal Cytomegalovirus Transmission in Very Preterm Infants	Bapistella et al., 2019[19]	Germany/ 87 NB†	Assess the effectiveness of pasteurization to prevent the transmission of cytomegalovirus via breast milk in preterm infants.	Cohort/ Level IV	The short-term supply of pasteurized HM reduced the incidence of cytomegalovirus infection through breast milk in the NICU§.
A5	Risk Factors for Late-Onset Sepsis in Preterm Infants: A Multicenter Case-Control Study	Hassani et al., 2019[20]	Netherlands/ 755 NB†	Identify risk factors for late-onset sepsis in PTNB.	Case-control/ Level IV	Breast milk feeding has demonstrated a protective effect against the development of late-onset sepsis in PTNB, in addition to reducing the number of days of parenteral nutrition.
A6	Banked Human Milk and Quantitative Risk Assessment of Bacillus cereus Infection in Premature Infants: A Simulation Study	Lewin et al., 2018[24]	Canada/ 1,000 NB†	Estimate the potential risk of Bacillus cereus infection in premature neonates caused by ingestion of contaminated pasteurized stored HM using different post-pasteurization release criteria.	Non-randomized clinical trial/ Level III	The risk of ***Bacillus cereus*** infection after ingesting pasteurized HM is small. Even so, the importance of bacteriological investigation before distributing HM to extremely premature babies is highlighted.
A7	Human milk feeding and cognitive outcome in preterm infants: the role of infection and NEC reduction	Lapidaire et al., 2022[21]	England/ 926 NB†	Investigate associations between early diet, infection and long-term cognitive outcome.	Randomized clinical trial/ Level II	HM, whether expressed raw or donated pasteurized HM, protects premature babies against infection and necrotizing enterocolitis. Furthermore, the absence of these is associated with better results in intelligence and performance coefficients.

** LoE: level of evidence; †NB: newborns; ‡ PTNB: premature newborns; §NICU: Neonatal Intensive Care Unit; HM – human milk.*

Chart 2. Benefits of offering breast milk to premature newborns to control infections.

Effects of breastfeeding on premature newborns	Articles (n; %)
Decreased incidence of necrotizing enterocolitis	A2; A3; A7 (n=3; 42.85%)
Reduction of the inflammatory state	A1; A7 (n=2; 28.57%)
Late sepsis reduction	A3; A5 (n=2; 28.57%)
Promoting complete enteral nutrition	A1; A5 (n=2; 28.57%)
Increased weight gain	A1; A3 (n=2; 28.57%)
Decreased incidence of cytomegalovirus	A4 (n=1; 14.28%)
Risk of *Bacillus cereus* infection	A6 (n=1; 14.28%)

Regarding the reduction in the incidence of sepsis, a randomized double-blind clinical trial, carried out with 48 premature babies in Korea, presented similar data, by showing that oropharyngeal administration of colostrum can depress clinical sepsis, inhibit the secretion of pro-inflammatory cytokines as well as increase the levels of circulating immunoprotective factors in extremely premature infants.[29]

One hypothesis to answer this phenomenon caused by HM in the baby's body concerns its composition, rich in substances that act on the defense system, such as immunoglobulins, anti-inflammatory and immunostimulating factors. It is also rich in cytokines which, when in contact with receptors present in the mucosa of the gas-

trointestinal tract, contribute to defense mechanisms.[30]

Based on this information, it is theorized that colostrum therapy is a protective action against neonatal sepsis, specifically through the following mechanisms: "1) interaction of milk cytokines with oropharyngeal immune cells, 2) absorption of protective biofactors by the mucosa, 3) barrier protection against pathogens, 4) local and systemic effects of oligosaccharides that modulate the intestinal microbiota and 5) beneficial effect of antioxidant protection".[31]

Regarding the reduction in the incidence of necrotizing enterocolitis, the data also prove true when comparing HM use with specific formula for premature babies, as, when assessing studies with more than 15,000 babies, a meta-analysis concluded that the use of 100% human milk can reduce by up to 4% in any type of disease, and by 2% in the most severe cases.[32] It is also believed that, when ingesting colostrum, it starts to shape the intestinal microbiota, thus reducing the risks for the development of necrotizing enterocolitis.[33]

Still talking about the diseases that can affect this public, the positive effects of HM on the lungs are also allies against bronchopulmonary dysplasia (BD). This is due to the antioxidant properties present in HM, which can contribute to a better prognosis of the disease, acting in oxidative stress prevention, one of the factors causing BD, and in the treatment of lung lesions.[34]

However, it is necessary to clarify that it is not enough to simply keep the PTNB on a HM diet, as it is essential to achieve an adequate caloric balance in order to meet their energy needs. An inadequate supply of nutrients increases damage to the alveoli, while, if done properly, it allows for the development and maturation of the lungs as well as the repair of injuries already present.[35,36]

Further, with regard to the reduction in the incidence of cytomegalovirus, despite the literature pointing out that its transmission is characterized as a common cause of maternal-fetal infection, it is consensual that, even if their mothers are seropositive for cytomegalovirus, full-term newborns must be breastfed.[37,38]

This may be explained by the fact that the composition of HM varies depending on the stage of lactation and the mother's serological status. This biological property makes it possible to partially neutralize virus and bacterial particles; in this way, it reduces the risk of transmission of infectious viruses to PTNBs.[39]

In this same paradigm, there is a risk of infection by Bacillus cereus when feeding the PTNB with stored HM, cited by an article (n=1; 14.28%). It was observed, in a French study, that this bacterium is the most frequent pathogen found in HM, stored in Human Milk Banks, being the main cause of discard[40]. Therefore, bacteriological investigation is essential before distributing HM to extremely premature newborns.

In addition to acting against diseases, HM also acts in other essential areas that surround the life of PTNB, such as promoting complete enteral nutrition and increasing weight gain. HM has a high nutritional content, as it contains lipids, proteins, vitamins, enzymes and minerals, making it the most suitable food for this audience, as it favors their physiological, biological and immunological development, enabling better results in intelligence and performance coefficients.[21]

The study has as a limitation the variety of methodological designs identified among the studies, such as case-control, cohort, cross-sectional studies and clinical trials, which does not allow for an in-depth comparison of their results.

In this scenario, it is essential that health services and professionals involved in practical and managerial activities develop policies and implement strategies capable of promoting the practice of breastfeeding in neonatal units aiming to prevent infections and, consequently, infant mortality.

CONCLUSION

It was evident that breastfeeding has a positive relationship with infection control in PTNB by promoting several benefits that reduce the risk of this condition appearing. The articles analyzed demonstrate that maternal HM is capable of reducing the incidence of necrotizing enterocolitis and cytomegalovirus, reducing the worsening of inflammatory states and late-onset sepsis, preventing diseases such as bronchopulmonary dysplasia as well as stimulating the physical development of PTNBs.

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AUTHORS' CONTRIBUTIONS

Raphaella Castro Jansen, Maria Rayssa do Nascimento Nogueira, Vitória Talya dos Santos Sousa, Vitoria Costa Oliveira contributed to article conception and design, data analysis and manuscript writing. **Anne Fayma Lopes Chaves** contributed to data analysis and interpretation.

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Revista de Epidemiologia e Controle de Infecção

Hospital Santa Cruz

CASE REPORT

Community-acquired neonatal SARS-CoV-2 infection: case report

Infecção neonatal por SARS-CoV-2 adquirida na comunidade: relato de caso

Infección neonatal por SARS-CoV-2 adquirida en la comunidad: reporte de caso

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Corresponding Author:
Dulciane Nunes Paiva
dulciane@unisc.br

Endereço: Avenida Independência, 2293, Santa Cruz do Sul – RS. CEP: 96815-900. Bloco 42 - Programa de Pós-Graduação Mestrado e Doutorado em Promoção da Saúde (PPGPS).

Kamila Mohammad Kamal Mansour[1];
Bruna Eduarda Diehl[1];
Fabiana Rafaela Santos de Mello[1];
Daniela Miranda Uroda[1];
Rafik Ali Juma Hamid[1];
Éboni Marília Reuter[1];
Dulciane Nunes Paiva[1];

[1] *Universidade de Santa Cruz do Sul (UNISC), Santa Cruz do Sul, RS, Brasil.*

ABSTRACT

Background and Objectives: Data collection on the incidence of COVID-19 is conducted less frequently in newborns (NB) than in adults. In view of the small number of described neonatal SARS-CoV-2 infections, in this study, we report a clinical case of community-acquired COVID-19 infection in a newborn. **Methods:** Clinical characteristics were collected from the medical records from April 2021 until the final outcome of the newborn in May 2021. **Results:** This article discusses the case of a full-term male newborn aged 38 weeks. On the 17th day of life, this newborn was admitted to the pediatric unit with fever and zone 4 jaundice, mild lower chest retraction and tachypnea. The mother was diagnosed with COVID-19. Late neonatal sepsis with pulmonary focus was detected. The newborn was hospitalized and the antigen test for COVID-19 came back positive. The condition of the neonate rapidly deteriorated and he was referred to the neonatal intensive care unit (NICU), where he was intubated and placed on pressure-controlled mechanical ventilation. During his second week in the NICU, he developed severe pulmonary hypertension with decreased peripheral oxygen saturation and tachycardia. The newborn required blood transfusion and was put into prone position during part of the treatment. Reductions in mechanical ventilation parameters were not tolerated by the NB's organism and he developed progressive hypoxemia. The newborn died 1 month and 3 days after hospitalization. **Conclusion:** Our study shows a case of community-acquired COVID-19 that progressed to the severe form of the disease.

Keywords: *COVID-19. SARS-CoV-2. Neonatal Intensive Care. Communicable Diseases, Emerging.*

RESUMO

Justificativa e Objetivos: A coleta de dados sobre a ocorrência de covid-19 em recém-nascidos (RN) não é tão frequente quanto em adultos. Portanto, devido ao baixo número de infecções neonatais por SARS-CoV-2 descritas, relatamos, neste estudo, um caso clínico de infecção por covid-19 adquirida na comunidade em um recém-nascido.

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Métodos: As características clínicas foram coletadas dos prontuários desde abril de 2021 até o último desfecho do RN, em maio de 2021. **Resultados**: Este artigo abordará um RN do sexo masculino, a termo, com 38 semanas. No 17º dia de vida, o RN deu entrada na unidade pediátrica com quadro de febre e icterícia zona 4, leve retração torácica inferior e taquipneia. A mãe foi diagnosticada com covid-19. Foi detectada sepse neonatal tardia com foco pulmonar. O RN foi internado e o teste de antígeno para covid-19 foi positivo. O quadro do RN regrediu rapidamente, sendo encaminhado à unidade de terapia intensiva neonatal (UTIN), onde foi entubado e adaptado à ventilação mecânica em modo pressão controlada. Na segunda semana de internação na UTIN, desenvolveu hipertensão pulmonar grave com diminuição da saturação periférica de oxigênio e taquicardia. O RN necessitou de transfusão sanguínea e a posição prona foi realizada por períodos. Reduções nos parâmetros do ventilador mecânico não foram toleradas e o RN apresentou hipoxemia progressiva. O RN faleceu um mês e três dias após a internação. **Conclusão:** Nossos achados apresentam um caso de covid-19 adquirida na comunidade que evoluiu para a forma grave da doença.

Descritores: *Covid-19. SARS-CoV-2. Terapia Intensiva Neonatal. Doenças Transmissíveis Emergentes.*

RESUMEN

Justificación y Objetivos: La recolección de datos sobre los contagios por covid-19 en recién nacidos (RN) no es tan frecuente como en adultos. En este contexto, y debido al bajo número de infecciones neonatales por SARS-CoV-2 descritas, en este estudio se describe un caso clínico de infección posnatal por covid-19 en un recién nacido en la comunidad. **Métodos:** Se recogieron características médicas de las historias clínicas desde abril de 2021 hasta el último resultado del RN en mayo de 2021. **Resultados:** Este artículo reporta el caso de un RN del sexo masculino, a término de 38 semanas. Al 17.º día de vida, el RN ingresó a la unidad de pediatría con fiebre e ictericia zona 4, leve retracción torácica inferior y taquipnea. La madre dio positivo para covid-19. En el RN se detectó sepsis neonatal tardía con foco pulmonar. Lo hospitalizaron, y la prueba de antígenos para covid-19 dio como resultado positivo. El estado del RN empeoró rápidamente, lo remitieron a la unidad de cuidados intensivos neonatales (UCIN), donde requirió intubación y ventilación mecánica controlada por presión. En la segunda semana en la UCIN, desarrolló hipertensión pulmonar grave con disminución de la saturación periférica de oxígeno y taquicardia. El RN requirió transfusión sanguínea, y lo pusieron en posición prona por períodos. El paciente no soportó las reducciones en los parámetros del ventilador mecánico y presentó una hipoxemia progresiva. El RN falleció un mes y tres días después de la hospitalización. **Conclusión:** Los hallazgos muestran un caso del covid-19 adquirido en la comunidad que progresó a la forma grave de la enfermedad.

Palabras Clave: *COVID-19. SARS-CoV-2. Cuidado Intensivo Neonatal. Enfermedades Transmisibles Emergentes.*

INTRODUCTION

Neonatal Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) infection is uncommon but some life-threatening infections have been reported.[1] SARS-CoV-2 can infect newborns (NB) either from the environment (community-acquired) or from the pregnant mother *in utero* or *peripartum* during labor.[1,2] In children, COVID-19 infection rates are similar to those in adults, but with predominantly mild or asymptomatic manifestations. Transmission in children typically involves those with preexisting comorbidities, with only 1% requiring hospitalization, less than 0.02% requiring intensive care, and low mortality rates.[3]

Neonatal COVID-19 infections usually present mild symptoms, but in some cases, they develop into neonatal SARS-CoV-2 multisystem inflammatory syndrome, a more severe form of the disease[3] Data collection on the incidence of COVID-19 is conducted less frequently in newborns (NB) than in adults. In view of the small number of described neonatal SARS-CoV-2 infections, in this study, we report a clinical case of postnatal community-acquired COVID-19 infection in a newborn.

METHODS

This is an observational and prospective case report of a newborn admitted to a teaching hospital in southern Brazil. Clinical characteristics were collected from medical records. The study was conducted in accordance with the ethical standards established by the Ministry of Health Resolutions 466/2012, 510/2016 and 580/2018. Written informed consent was obtained from the NB's mother. The Research Ethics Committee of the University of Santa Cruz do Sul approved this study on April 9, 2021, under no. 4.641.390 and CAAE no. 45402221.5.0000.5343.

RESULTS

This is the case of a full-term male newborn (38 weeks), Apgar 9/9 and large for gestational age. He was born to a 24-year-old mother by Cesarean section with complete prenatal care. There were no complications during pregnancy and delivery, and the baby was discharged 48hs *post-partum*. The newborn was healthy, exclusively breastfed, and had normal physiological functions until the 17th day of life, when he was admit-

ted to the pediatric unit with fever (38.5°C) and zone 4 jaundice, mild lower chest retraction and tachypnea (65 breaths/min). The mother was diagnosed with COVID-19. The NB's medical records did not contain information on the mother's vaccination status.

Seven days after the onset of the mother's symptoms, the newborn became symptomatic. Community-acquired SARS-CoV-2 was suspected. The newborn was tested for other vertically transmitted infectious diseases, but all results were negative. Late neonatal sepsis with pulmonary focus was detected (Rodwell).[4] The newborn was subsequently hospitalized (Figure 1).

According to the protocol of the hospital, the imaging exams (Figure 2) and the antigen test for COVID-19—performed using a nasal swab—yielded positive results for COVID-19. The NB's condition rapidly deteriorated and he was referred to the neonatal intensive care unit (NICU) (Figure 3), where he was intubated and placed on pressure-controlled mechanical ventilation (MV).

Laboratory tests showed a d-dimer of 1,892.2 ng/mL, and prophylaxis with enoxaparin was started. The newborn had bacterial pneumonia confirmed by blood culture, the infection was diagnosed on his first day at the NICU. He was treated with oxacillin and amikacin. Based on positive blood cultures performed during hospitalization, he was also treated with vancomycin and cefepime, azithromycin, vancomycin, and meropenem. He presented hemodynamic instability/hypotension and severe pulmonary hypertension (PH). The newborn showed a decrease in peripheral oxygen saturation, as well as tachycardia and generalized edema.

The neonate required blood transfusions and underwent nitric oxide therapy for PH with unsatisfactory results. In addition, he received physical therapy three times per day and was put into prone position during part of the treatment. Reductions in MV parameters were not tolerated by his organism. On his last day of life, the newborn was pale, cyanotic, hypothermic and in anasarca. He developed progressive hypoxemia and died due to complications caused by COVID-19 infection (Table 1).

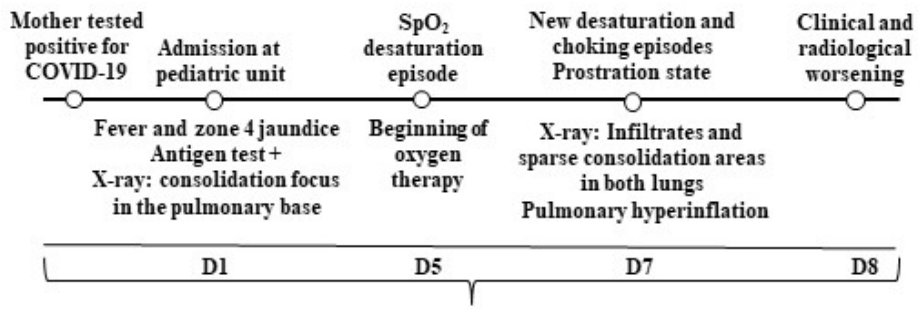

Figure 1. Timeline prior to admission to the neonatal intensive care unit.

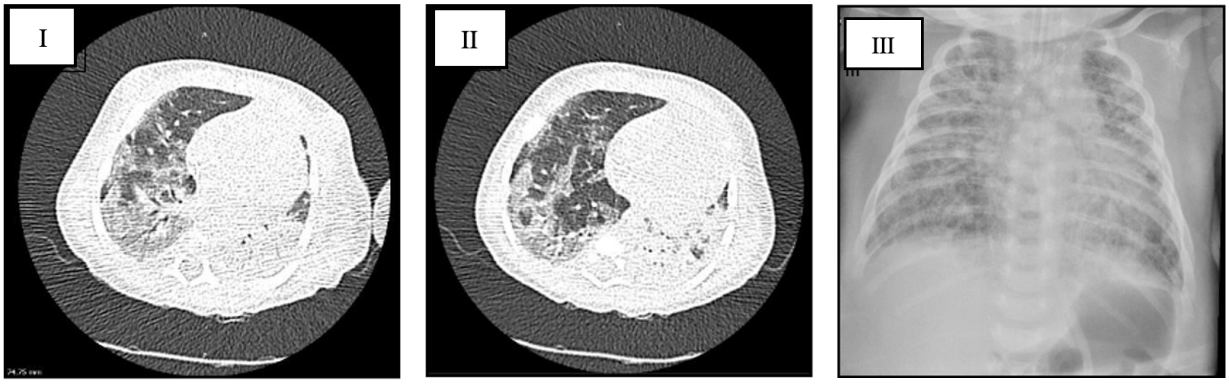

Figure 2. Chest computed tomography. Computed tomography (I and II) showing ground-glass opacities with reticulation (mosaic), multifocal, predominantly peripheral, affecting 50–75% of the parenchyma, accompanied by consolidations, typical alterations of viral pneumonia. Chest X-ray (III) showing diffuse and heterogeneous interstitial infiltrates affecting practically the entirety of both lungs. The image also shows bronchial wall thickening and pulmonary hyperinflation.

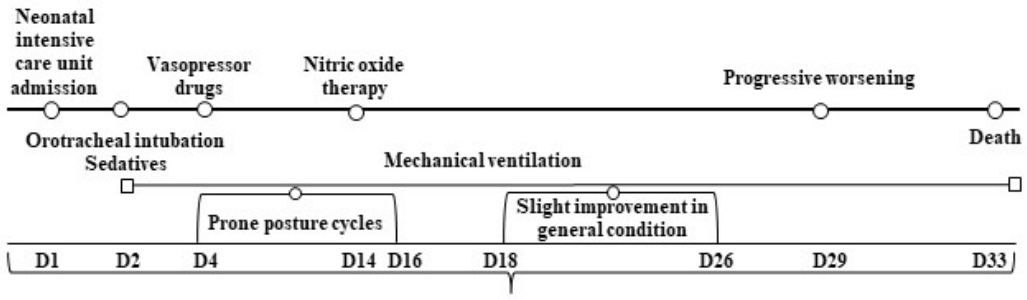

Figure 3. Timeline after admission to the neonatal intensive care unit.

Table 1. Arterial blood gas tests and ventilatory strategies used during key periods of the neonate's hospitalization in the neoatal intensive care unit.

NICU period	1st ND Admission	2nd ND	2nd ND	2nd ND	8th ND	18th ND	30th ND
Ventilatory strategy	LF (O2 3 l/min)	Campanula (15 l/min/80%)	HF (10 l/min/100%)	IMV (PCV 20×6/75%)	IMV (PCV 38×8/100%)	IMV (PCV 40×8/100%)	IMV (PCV 39×7/100%)
pH	7.36	7.40	7.37	7.36	7.38	7.53	7.24
PaO_2 (mmHg)	54.8	53.2	37.5	105.9	143.8	42.7	22.8
$PaCO_2$ (mmHg)	40.3	42.5	50.0	49.1	53.0	49.8	66.2
HCO_3 (mEq/l)	22.6	25.7	28.4	27.5	30.6	40.7	27.9
CO_2 (mmol/l)	23.9	27.1	29.9	29.0	32.2	42.2	29.9
EB (mEq/l)	−2.5	+0.8	+2.3	+1.5	+4.4	+15.4	−1.2
SaO_2 (%)	86.9	88.1	72.0	97.7	99.1	76.8	28.7
$RPaO_2/FiO_2$	228.3	52.9	37.5	141.2	143.0	42.7	22.8

NICU: Neonatal Intensive Care Unit; ND: NICU day; LF: low-flow oxygen therapy; HF: high flow; IMV: invasive mechanical ventilation; PCV: pressure-controlled ventilation; PaO_2 partial pressure of oxygen in arterial blood; $PaCO_2$: partial pressure of carbon dioxide in arterial blood; HCO_3: serum bicarbonate concentration; CO_2: carbon dioxide; BE: base excess; SaO_2: oxygen saturation; $RPaO_2/FiO_2$: ratio of arterial oxygen partial pressure to fractional inspired oxygen.

DISCUSSION

Our case report differs from the existing literature because the NB case described had severe repercussions of the disease, causing the infected newborn to be hospitalized. Towards the end of his illness, the newborn presented anasarca, hypotension, and severe hypoxemia.

NB can also be infected with coronavirus, although they are less susceptible to the severe form, and they usually have a good prognosis, as shown by a study published in 2020, which reported the case of a 17-day-old newborn who presented transient fever and diarrhea but did not develop serious complications.[5-7]

Cases of community-acquired transmission in this population can occur via close contact with infected individuals or breastfeeding. In NB, the presentation of COVID-19 tends to be asymptomatic or mild or does not differ from that of other neonatal diseases.[3]

Although the frequency of SARS-CoV-2 infection in neonates is extremely low, a portion of neonates affected by COVID-19 may present more severe symptoms, requiring intensive care, which indicates that the disease is more severe in newborns than in older children.[8]

Community-acquired cases are more likely to require hospitalization due to the presentation of the spectrum of clinical features of SARS-CoV-2 infection, including fever, respiratory symptoms and feeding difficulties, as seen in this case report.[9] We encourage the vaccination of pregnant women against the SARS-CoV-2 virus and further research on this topic in infected newborns.

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AUTHORS' CONTRIBUTIONS

Kamila Mohammad Kamal Mansour, Daniela Miranda Uroda, Éboni Marília Reuter, Dulciane Nunes Paiva contributed to the bibliographic research; writing of the abstract, introduction, methodology, discussion, interpretation and description of results, conclusions; revision of the manuscript; and preparation of tables and statistics. **Bruna Eduarda Diehl, Fabiana Rafaela Santos de Mello, Rafik Ali Juma Hamid** contributed to the bibliographic research; writing the abstract, introduction, methodology, discussion, conclusion; and revision of the manuscript.

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