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

ORIGINAL ARTICLE

Individual and contextual determinants of COVID-19 mortality in Pernambuco: a case-control study

Determinantes individuais e contextuais da mortalidade por COVID-19 em Pernambuco: estudo caso-controle

Determinantes individuales y contextuales de la mortalidad por COVID-19 en Pernambuco: un estudio de casos y controles

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Corresponding Author:
Maria Tatiane Alves da Silva
mtatianealves@hotmail.com

Address: Avenida Professor Moraes Rego, s/n, Cidade Universitária. Recife, PE, Brasil. CEP: 50740-465

Maria Tatiane Alves da Silva[1];
Lívia Teixeira de Souza Maia[2];
Gabriella Morais Duarte Miranda[1];
Ana Lúcia Andrade da Silva[1];

[1] *Instituto Aggeu Magalhães/Fundação Oswaldo Cruz, Recife, Pernambuco, Brazil.*
[2] *Universidade Federal de Pernambuco (UFPE), Recife, Pernambuco, Brazil.*

ABSTRACT

Background and Objectives: to analyze individual and contextual factors associated with mortality from COVID-19 in the state of Pernambuco. **Methods:** a case-control study, with secondary data from the Center for Strategic Information on Health Surveillance in Pernambuco (CIEVS-PE - *Centro de Informações Estratégicas de Vigilância em Saúde de Pernambuco*), where cases were deaths from COVID-19 and controls were those recovered. To develop the multilevel analysis, hierarchical regression listed the individual and contextual levels (healthcare and municipality), considering a statistical significance of 10%. **Results:** the study presented 18,198 cases and 27,647 controls, and the final model indicated 13 variables as determining factors for mortality in the state, ten of which were at the individual level (sex, age group, symptoms, O2 saturation <95%, respiratory distress, dyspnea, comorbidities, heart or vascular diseases, diabetes and obesity). At the contextual level, three variables were identified, two of which were related to healthcare (adult Intensive Care Unit beds and respirators/ventilators) and one to the municipality (health macroregion). **Conclusion:** the individual-level factors presented showed a greater determination for death by COVID-19 in the state of Pernambuco, making it necessary to reinforce healthcare for the most vulnerable groups.

Keywords: *COVID-19. Mortality. Social Determinants of Health. Health Inequality Monitoring.*

RESUMO

Justificativa e Objetivos: analisar os fatores individuais e contextuais associados à mortalidade por COVID-19 no estado de Pernambuco. **Métodos:** estudo de caso-controle, com dados secundários do Centro de Informações Estratégicas de Vigilância em Saúde de Pernambuco (CIEVS-PE), onde os casos foram os óbitos por COVID-19 e os

controles foram os recuperados. Para o desenvolvimento da análise multinível, a regressão hierárquica elencou os níveis individual e contextual (assistência à saúde e município), considerando a significância estatística de 10%. **Resultados:** o estudo apresentou 18.198 casos e 27.647 controles, sendo que o modelo final indicou 13 variáveis como fatores determinantes para mortalidade no estado, sendo dez do nível individual (sexo, faixa etária, sintomas, saturação O2<95%, desconforto respiratório, dispneia, comorbidades, doenças cardíacas ou vasculares, diabetes e obesidade). No nível contextual, foram identificadas três variáveis, sendo duas da assistência à saúde (leitos de Unidade de Terapia Intensiva adulto e respiradores/ventiladores) e uma do município (macrorregião de saúde). **Conclusão:** os fatores de nível individual apresentaram uma maior determinação para o óbito por COVID-19 no estado de Pernambuco, tornando-se necessário reforçar o cuidado em saúde para os grupos mais vulneráveis.

Descritores**:** *COVID-19. Mortalidade. Determinantes Sociais da Saúde. Monitoramento das Desigualdades em Saúde.*

RESUMEN

Justificación y Objetivos: analizar los factores individuales y contextuales asociados a la mortalidad por COVID-19 en el estado de Pernambuco. **Métodos:** estudio de casos y controles, con datos secundarios del Centro de Informaciones Estratégicas de Vigilancia de la Salud de Pernambuco (CIEVS-PE - *Centro de Informações Estratégicas de Vigilância em Saúde de Pernambuco*), donde los casos fueron las muertes por COVID-19 y los controles los recuperados. Para desarrollar el análisis multinivel, la regresión jerárquica enumeró los niveles individual y contextual (atención de salud y municipio), considerando una significación estadística del 10%. **Resultados:** el estudio presentó 18,198 casos y 27,647 controles, y el modelo final indicó 13 variables como factores determinantes de la mortalidad en el estado, diez de las cuales fueron a nivel individual (sexo, grupo etario, síntomas, saturación de O2 <95%, malestar respiratorio, disnea, comorbilidades, enfermedades cardíacas o vasculares, diabetes y obesidad). A nivel contextual se identificaron tres variables, dos de atención a la salud (camas de Unidad de Cuidados Intensivos de adultos y respiradores/ventiladores) y una del municipio (macrorregión de salud). **Conclusión:** factores a nivel individual presentados mayor determinación por la muerte por COVID-19 en el estado de Pernambuco, por lo que fue necesario reforzar la atención en salud a los grupos más vulnerables.

Palabras clave: *COVID-19. Mortalidad. Determinantes Sociales de la Salud. Monitoreo de las Desigualdades en Salud.*

INTRODUCTION

At the end of 2019, the Chinese government reported cases of pneumonia with an unknown etiological agent in the population, with the first cases being recorded in the city of Wuhan, China. The agent was later identified as a new coronavirus of Severe Acute Respiratory Syndrome (SARS), and was named SARS-CoV-2. The new coronavirus is responsible for the development of Coronavirus Disease 2019 (COVID-19), characterized as an infectious disease that affects individuals with mild or severe symptoms.[1,2]

Due to the high transmissibility and mortality, the World Health Organization (WHO) declared a Public Health Emergency of International Concern.[3] In Brazil, the first cases were registered in February 2020, and a Public Health Emergency of National Concern was declared. In this context, the main preventive measure adopted was social distancing, culminating in the so-called lockdown in the main Brazilian cities. The measure included the blocking of borders, the cancellation of cultural events and the temporary closure of businesses and educational institutions.[4,5]

Epidemiologically, by the end of March 2023, confirmed cases of COVID-19 had already surpassed 600 million worldwide, with more than 6 million deaths recorded. In the world ranking, Brazil was one of the countries with the most registered cases, accumulating more than 30 million cases and 650 thousand deaths. Regarding the distribution of morbidity and mortality from the disease in the national territory, the Southeast and Northeast regions stand out in absolute numbers, with the state of Pernambuco recording a total of more than 1 million cases and 20 thousand deaths.[6,7]

In Brazil, the distribution of infectious diseases across the territory has always been marked by immense social inequality.[8] Regarding COVID-19, the spread of the disease occurred with different magnitudes and effects in different population groups, in which socioeconomic determinants were found to be possible risk factors. The presence of inequalities reinforces an unfair scenario for the most vulnerable population, implying barriers to access to healthcare services and indicating that, in addition to the COVID-19 pandemic, the population faces an epidemic of social inequities.[9,10]

Therefore, the dimension of health inequalities permeates the issue of mortality from COVID-19, and the use of different analytical strategies can contribute to a more concrete statement about the association between risk factors and the determination of mortality. The use of multilevel models is an alternative to traditional multivariate models, considering the hierarchical nature present in the data and analyzing the autocorrelation between the risk factors of a given condition at the aggregation levels.[11,12]

From this perspective, the present study aimed to analyze the individual and contextual factors associated with mortality from COVID-19 in the state of Pernambuco.

METHODS

This is a case-control study with secondary data and a multilevel approach. The study used severe cases of SARS due to COVID-19 registered at the *Centro de Informações Estratégicas da Vigilância em Saúde de Pernambuco* (CIEVS-PE, Strategic Information Center for Health Surveillance of Pernambuco), between March 2020 and March 2022, being residents of the state of Pernambuco.

CIEVS/PE is one of the units of the Brazilian National Network for Monitoring and Response to Public Health Emergencies, and is responsible for the process of detecting, monitoring and coordinating the response to public health emergencies. In this context, it is made up of mandatory notifications, outbreaks and epidemics as well as events with health impact.[13]

For the study, confirmed deaths were considered cases, while controls were made up of recovered individuals. To compose the study sample, the inclusion criteria were to have the records made available by CIEVS/PE and to have the fields of independent variables filled in. Regarding the exclusion criteria, records without the final classification and the *Cadastro Nacional de Estabelecimentos de Saúde* (CNES, Brazilian National Registry of Health Establishments) number of the establishments were not considered.

Death from COVID-19 was considered as a dependent variable, and independent variables were allocated at the individual and contextual levels (subdivided into two levels, healthcare and municipalities).

Individual-level variables consisted of data made available in CIEVS-PE for each individual, such as sex, age group, presence of symptoms, O2 saturation <95, respiratory discomfort, dyspnea, presence of comorbidities, obesity, diabetes, and heart or vascular diseases.

The first contextual level (healthcare) consisted of data related to the hospital where a patient was admitted, made available in CNES, such as the establishment's legal nature, number of Adult Intensive Care Unit (ICU) beds and number of respirators/ventilators. To define the categories of Adult ICU beds and respirators/ventilators, the average of the period analyzed was considered, and the K-means method was used, which is used to construct automatic data groupings based on the degree of similarity (clusters).[14]

Therefore, for both variables, the units were grouped into three clusters (low, medium and high). Regarding Adult ICU beds, the low (0-3 beds), medium (4-44 beds) and high (> 45 beds) clusters were considered. While for ventilators/respirators, the low (0-4 ventilators/respirators), medium (5-50 ventilators/respirators) and high (> 51 ventilators/respirators) clusters were considered.

The second contextual level (municipality) was composed of the individuals' health macro-region of residence (I - Recife, II - Caruaru, III - Serra Talhada, IV - Petrolina), obtained from CIEVS-PE and the *Centro de Integração de Dados e Conhecimentos para Saúde* (CIDACS, Center for Data and Knowledge Integration for Health) Social Inequalities Index (COVID-19-SII), which is characterized as a marker of inequalities associated with COVID-19 formed by socioeconomic, sociodemographic information and difficulties in accessing healthcare services, being divided into very low, low, medium, high and very high.[15]

Initially, univariate analysis was performed to identify the association between the outcome (death from COVID-19) and each independent variable, calculating the Unadjusted Odds Ratio (Unadjusted OR) and its respective 95% Confidence Intervals (95% CI), in addition to statistical significance (p-value), based on the chi-square test (χ^2). For multivariate analysis, the regression included the independent variables that presented statistical significance below 20% ($p < 0.20$).

The multilevel model used in this study was adjusted using Generalized Linear Latent and Mixed Models (GLLAMM), considering information related to individuals as the first level, the hospital of admission as the second level, and adjustment for the municipality of residence (third level). This type of three-level model allowed estimating the measures of association between exposures and outcomes, considering that observations (individuals) taken within the same group (contexts) are not independent.

At this stage, the model was adjusted using the stepwise method. Thus, the model began with all significant variables in the bivariate model, and then variables whose statistical significance was greater than 10% ($p > 0.10$) were removed (a process called backward). Finally, to assess the quality of regression models, the study used the Akaike criterion (AIC) and the Bayesian Information Criterion (BIC) for all stages of multivariate analysis. The best models were those that presented results with the lowest AIC and BIC values.

In descriptive data analysis and processing, the Microsoft Excel 2013 spreadsheet editor was used to store the database, and the Data Analysis and Statistical Software (STATA) version 12.0 was used to develop the statistical analyses.

The study was approved by the Research Ethics Committee, under *Certificado de Apresentação para Apreciação Ética* (CAAE, Certificate of Presentation for Ethical Consideration) 60944122.8.0000.5190 and Opinion 5.652.161.

RESULTS

Table 1 presents the number and proportion of cases and controls at the first level (individual) according to variables, where the absolute number was 18,198 cases and 27,647 controls. Regarding individuals' sex, there is a predominance of men: 53.25% in cases and 54.33% in controls.

Concerning age group, it was observed that both groups had a greater predominance of individuals under 60 years of age, however, with high proportional differences. In cases, the proportion was 30.45%, and in controls,

it was 61.71%. Still regarding age group, it was observed that the most advanced ages (80 years or older) were those that presented the lowest proportion of controls, i.e., individuals who were diagnosed with SARS due to COVID-19 and recovered (Table 1).

In relation to symptoms, the results indicate that they were present in almost all individuals. In cases and controls, the proportion was higher than 98%. When analyzing the presence of symptoms (O2 saturation <95%, respiratory discomfort and dyspnea), it is noted that cases presented a higher proportion than controls (Table 1).

Regarding comorbidities, there was a difference between the groups. In the cases, the predominant presence was the presence of some comorbidity, being 66.15%, while, in the cases, the absence was more predominant, with a proportion of 57.90%. When analyzing the presence of comorbidities (heart or vascular diseases, diabetes and obesity) separately, it is noted that, in both groups, the absence was more predominant. However, in general, the proportions of the presence of these comorbidities were higher in cases when compared to controls (Table 1).

Table 2 presents data on the variables of the level of healthcare, containing the number and proportion of cases and controls. As for the legal nature, it was found that the majority of establishments had a link with the *Sistema Único de Saúde* (SUS, Brazilian Health System), being private or public. Approximately 72.66% of the cases occurred in public SUS establishments, while controls were 66.60%.

Concerning the number of adult ICU beds available, in both groups, it is worth noting that establishments with a number considered average (4 to 44 beds) presented the highest number of cases (53.12%) and controls (45.08%) (Table 2).

Regarding the number of ventilators/respirators, similar results were observed. The value considered average (5 to 50 ventilators/respirators) was the category that presented the highest proportion of cases and controls, equivalent to 52.62% and 51.12%, respectively (Table 2).

Table 1. Number and proportion of cases and controls and p-value of individual-level variables. Pernambuco, March 2020 to March 2022.

Variables	Cases		Controls		p-value
	N	%	N	%	
Sex					
Female	8,507	46.75	12,627	45.67	0.024
Male	9,691	53.25	15,020	54.33	
Age range					
Under 60 years	5,542	30.45	17,062	61.71	0.000
60 to 69 years	3,971	21.82	4,748	17.17	
70 to 79 years	4,409	24.23	3,502	12.67	
80 years old or older	4,276	23.5	2,335	8.45	
Symptoms					
Absent	252	1.38	467	1.69	0.010
Present	17,946	98.62	27,180	98.31	
O2 saturation<95%					
Absent	4,674	25.68	10,088	36.49	0.000
Present	13,524	74.32	17,559	63.51	
Respiratory discomfort					
Absent	9,595	52.73	17,558	63.51	0.000
Present	8,603	47.27	10,089	36.49	
Dyspnea					
Absent	3,441	18.91	6,986	25.27	0.000
Present	14,757	81.09	20,661	74.73	
Comorbidities					
Absent	6,160	33.85	16,007	57.9	0.000
Present	12,038	66.15	11,640	42.1	
Heart or vascular disease					
Absent	10,230	7.968	21,054	76.15	0.000
Present	56.21	43.79	6,593	23.85	
Diabetes					
Absent	12,494	68.66	22,828	82.57	0.000
Present	5,704	31.34	4,819	17.43	
Obesity					
Absent	16,468	90.49	25,835	93.45	0.000
Present	1,730	9.51	1,812	6.55	

Source: prepared by the author based on data from CIEVS-PE (2020 to 2022).

Table 2. Number and proportion of cases and controls and p-value of healthcare level variables. Pernambuco, March 2020 to March 2022.

Variables	Cases		Controls		
	N	%	N	%	p-value
Legal nature					
Private non-SUS	1,433	7.87	1,945	7.04	0.000
Private SUS	3,389	18.62	7,017	25.38	
Public non-SUS	153	0.84	273	0.99	
Public SUS	13,223	72.66	18,412	66.6	
ICU beds					
High (>45)	4,686	25.75	7,987	28.89	0.010
Medium (4-44)	9,667	53.12	12,463	45.08	
Low (0-3)	3,845	21.13	7,197	26.03	
Ventilators/respirators					
High (>51)	5,194	28.54	7,360	26.62	0.000
Medium (5-50)	9,576	52.62	14,133	51.12	
Low (0-4)	3,428	18.84	6,154	22.26	

Note: SUS – Brazilian Health System; ICU – Intensive Care Unit.
Source: prepared by the author based on data from CIEVS-PE (2020 to 2022).

In Table 3, it is possible to observe the results of bivariate analysis related to the municipality level. Regarding COVID-19-SII, it is noteworthy that the predominance of cases (34.58%) and controls (34.85%) was in the category listed as a high index.

As for the location of residence of individuals, it is noted that the majority of the proportion of cases and controls was concentrated in health macroregion I (Recife), with a total of 69.91% and 67.00%, respectively (Table 3).

Table 3. Number and proportion of cases and controls and p-value of variables at the municipal level. Pernambuco, March 2020 to March 2022.

Variables	Cases		Controls		
	N	%	N	%	p-value
COVID-19 Social Inequality Index					
Very low	5,159	28.35	7,658	27.7	0.683
Low	0	0	0	0	
Medium	1,496	8.22	2,510	9.08	
High	6,293	34.58	9,635	34.85	
Very high	5,250	28.85	7,844	28.37	
Health macroregion					
I (Recife)	12,723	69.91	18,523	67	0.000
II (Caruaru)	2,796	15.36	4,130	14.94	
III (Serra Talhada)	1,288	7.08	1,842	6.66	
IV (Petrolina)	1,391	7.64	3,152	11.4	

Source: prepared by the author based on data from CIEVS-PE (2020 to 2022).

Table 4 presents the consolidation of the final results of the multilevel model for the association between mortality from COVID-19 and individual and contextual determinants in the state of Pernambuco. Initially, the model consisted of 15 variables, of which only two did not make up the final model: one from the level of healthcare (legal nature) and one from the municipal level (COVID-19-SII).

The individual level was composed of ten variables, showing a statistical association with the final outcome and all with p = 0.000. The level of healthcare was composed of two variables: number of Adult ICUs and number of ventilators/respirators. Meanwhile, the municipal level was composed only of the variable referring to the health macroregion (Table 4).

In Pernambuco, being male (OR = 1.17) and aged 80 years or older (5.65) represented a risk factor for mortality from COVID-19. In the symptom variables, it is noteworthy that the presence of O2 saturation <95% was characterized as the greatest risk factor, being 1.56 times higher. However, the presence of respiratory distress and dyspnea was also found to be a risk factor, with an adjusted OR of 1.45 and 1.31, respectively. The presence of comorbidities (adjusted OR = 1.71) was also found to be a risk factor, with the presence of obesity (1.36) also standing out (Table 4).

Concerning healthcare, individuals admitted to establishments belonging to the medium category of the number of Adult ICU beds and ventilators/respirators had a higher chance of death from COVID-19.

The health macroregion variable was the only one at the municipal level that remained in the final model, which presented an adjusted OR lower than 1.

Table 4. Adjusted Odds Ratio, Confidence Interval and significance (p-value) values obtained through multilevel analysis. Pernambuco, March 2020 to March 2022.

Variables	AdjustedOR	CI	p-value
Sex			
Female	1	-	-
Male	1.17	1.12-1.23	0.000
Age range			
Under 60 years	1	-	-
60 to 69 years	2.22	2.10-2.36	0.000
70 to 79 years	3.48	3.27-3.70	0.000
80 years or older	5.65	5.28-6.04	0.000
Symptoms			
Absent	1	-	-
Present	0.65	0.54-0.78	0.000
O2 saturation<95%			
Absent	1	-	-
Present	1.56	1.48-1.65	0.000
Respiratory discomfort			
Absent	1	-	-
Present	1.45	1.39-1.53	0.000
Dyspnea			
Absent	1	-	-
Present	1.31	1.24-1.39	0.000
Comorbidities			
Absent	1	-	-
Present	1.71	1.59-1.83	0.000

Heart or vascular diseases			
Absent	1	-	-
Present	1.31	1.23-1.39	0.000
Diabetes			
Absent	1	-	-
Present	1.17	1.10-1.24	0.000
Obesity			
Absent	1	-	-
Present	1.36	1.25-1.48	0.000
Adult ICU beds			
Absent	1	-	-
Present	1.25	1.12-1.39	0.000
Absent	0.85	0.71-1.02	0.088
Ventilators/respirators			
Present	1	-	-
High (>45)	0.86	0.78-0.96	0.006
Medium (4-44)			
Health macroregion	0.66	0.56-0.79	0.000
I (Recife)	1	-	-
II (Caruaru)	0.97	0.87-1.09	0.688
III (Serra Talhada)	0.87	0.74-1.02	0.088
IV (Petrolina)	0.77	0.64-0.94	0.010

Note: number of units at level 1: 45,763; number of units at level 4,176; number of units at level 183; Model adjustment: AIC 51029.06 / BIC 51221.15; level 2 (adjusted by the health facility), variance 0.50762424 (0.03671655); level 3 (adjusted by the municipality), variance: 8.92700000 (3.18200000); ICU – Intensive Care Unit; CI – Confidence Interval.
Source: prepared by the author based on data from CIEVS-PE (2020 to 2022).

DISCUSSION

The results obtained in the present study showed that the individual level presented greater determining factors with mortality from COVID-19 in the state of Pernambuco, highlighting men, age group of 80 years or older, presence of symptoms, comorbidities, O2 saturation <95%, respiratory discomfort, dyspnea, heart or vascular diseases, diabetes and obesity.

In Pernambuco, there was a predominance of cases and controls in the male population, where men had a 17% higher chance of death. In a study conducted in the state of Rio Grande do Norte, the results indicate that being male was found to be a risk factor for mortality from the disease, with men having a 45% higher chance of death than women; therefore, they had a lower chance of survival.[16] A meta-analysis study found that the number of cases and fatality rates were more prevalent in the male population.[17]

From this perspective, it is worth noting that the chances of men dying more than women from COVID-19 can be characterized as a warning sign, and may present multivariate factors. However, the identification and recognition of this mortality factor are essential to support public policies and actions aimed at combating the disease, with ensuring equal access to healthcare services being a crucial device for men's healthcare.

Older adults aged 80 years or older presented a higher risk of death from COVID-19, as was observed for the fatality rates from the disease.[18] The pandemic attenuated the social inequalities that exist in the various scenarios in the country, being deepened in the most vulnerable older adults. The permanence in economic activities and in remote mode was found to be a barrier for this population. From this perspective, in addition to health, the pandemic brought about a series of social consequences.[19]

The presence of symptoms was predominant in both groups (cases and controls), being a determining factor for death, a similar result in a study that indicated cough, myalgia and other respiratory signs as the most frequent symptoms in the population.[20] However, it is noteworthy that the present study presents a prevalence of symptoms, as it is a study with a database of serious and hospitalized cases. This fact may have influenced the lack of differentiation between case and control groups, since almost all cases that generate hospitalization are symptomatic individuals.

Still regarding the presence of symptoms, individuals who presented O2 saturation <95%, respiratory distress and dyspnea had a higher risk of death in the state of Pernambuco. In Recife, the state capital, results indicate similar findings, where severe respiratory symptoms were also associated with death in the city.[21] Respiratory symptoms have also been identified in patients worldwide, such as the presence of dyspnea.[17] From this perspective, continuous monitoring of symptoms, through different strategies, is a strategy for preventing worsening and death from the disease.[22]

The presence of comorbidities as a risk factor was more prevalent in the case group than in the control group. Among the comorbidities analyzed in the study, heart or vascular diseases and diabetes were the ones that presented the highest proportions in the case group. In a cohort study carried out to identify the clinical characteristics of patients diagnosed with COVID-19, it was found that the presence of some comorbidity was more prevalent in deaths (48%) than in those who recovered (14%), with cardiovascular diseases standing out.[23]

This population requires differentiated healthcare, in which mapping these individuals can be a fundamental tool for healthcare. In this context, the pandemic reaffirmed the importance of coordination between health surveillance services and Primary Care, with multidisciplinary and interdisciplinary action constituting one of the main healthcare strategies within SUS.[24]

At the contextual level, in the context of healthcare, the number of ICU beds was found to be a determining factor in mortality, with individuals admitted to facilities with the average number of beds having the highest risk. Sometimes, hospitals with the highest number of beds received patients with the most critical conditions, which can increase mortality rates in these facilities. A national survey found that the health regions with the highest mortality rates were marked by a shortage of beds and equipment.[25] However, it is worth noting that the present study did not necessarily seek to analyze the availability of beds and ventilators/respirators, but rather the dimen-

sion of healthcare.

As for the second contextual level, initially, due to the history of social disparities in the distribution of infectious and parasitic diseases, the presence of higher risk variables was expected, but this result was not observed. This result may indicate that proximal (individual) factors are stronger than distal (contextual) factors. However, this finding does not imply that there is no association between COVID-19 and the context of individuals. The pandemic has led to the development of several studies, with different methodological approaches, with the source of information being one of the main differences between the studies.

Therefore, this result points to the need for future studies that consider other contextual variables and methodologies. Even with the advancement of coverage and quality of health information systems, limitations regarding the completion and completeness of variable records are constant. However, despite the limitations exposed, the construction of research based on secondary databases allows the development of longitudinal studies with a low operational cost.

Given the scenario identified in the results of this study, it is essential to humanize the data. The deaths that occurred in the state of Pernambuco are not just epidemiological numbers, but information about individuals with names, families and stories. Part of the Brazilian population died because the right to life was denied, mainly due to living conditions and access to healthcare services.

The fight against COVID-19 and the search for improvements in the quality of life of the population of the state of Pernambuco necessarily involve strengthening SUS as the main state policy for guaranteeing citizenship and the right to health, reducing social inequalities and inequities. Finally, the pandemic has exposed the Brazilian health system weaknesses, but it has also made clear the greatness of SUS.

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AUTHORS' CONTRIBUTIONS

Maria Tatiane Alves da Silva contributed to bibliographic research, abstract writing, introduction, methodology, discussion, interpretation and description of results, preparation of tables, conclusions, review and statistics. **Lívia Teixeira de Souza Maia** contributed to project management, bibliographic research, abstract writing, introduction, methodology, discussion, interpretation and description of results, conclusions, review and statistics. **Gabriella Morais Duarte Miranda** contributed to bibliographic research, abstract writing, introduction, methodology, discussion, interpretation and description of results, preparation of tables, conclusions, review and statistics. **Ana Lúcia Andrade da Silva** contributed to bibliographic research, abstract writing, introduction, methodology, discussion, interpretation and description of results, preparation of tables, conclusions, review and statistics.

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ORIGINAL ARTICLE

Temporal analysis of notified cases of American cutaneous leishmaniasis in the state of Piauí, Brazil (2007-2022)

Análise temporal dos casos notificados de leishmaniose tegumentar americana no estado do Piauí, Brasil (2007-2022)

Análisis temporal de casos notificados de leishmaniasis cutánea americana en el estado de Piauí, Brasil (2007-2022)

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Corresponding Author:
Henrique Rafael Pontes Ferreira
henrique.pontes@ufpe.br

Av. Reitor Joaquim Amazonas, Cidade Universitária, 50740600 - Recife, PE – Brasil.

Daniela Soares Leite[1];
Jamileh Marinho de Carvalho[2];
Maura de Souza Pereira Portilho[3];
Marcela Bezerra Dias[4];
Kleberson de Oliveira[5];
Henrique Rafael Pontes Ferreira[6];

[1] *Universidade do Estado do Pará (UEPA), Belém, PA, Brasil.*
[2] *Universidade Estadual de Mato Grosso do Sul (UEMS), Dourados, MS, Brasil.*
[3] *Faculdade Gamaliel, Tucuruí, PA, Brasil.*
[4] *Universidade Estadual Paulista (UNESP), São Paulo, SP, Brasil.*
[5] *Universidade Federal do Triângulo Mineiro (UFTM), Uberaba, MG. Brasil.*
[6] *Universidade Federal de Pernambuco (UFPE), Recife, PE, Brasil.*

ABSTRACT

Background and Objectives: American tegumentary leishmaniasis (ATL) is a public health concern, and its control remains a challenge in territories with significant social vulnerability. Piauí is one of the most socially vulnerable states in Brazil, and knowing the profile of notifications can serve as support in the implementation of more efficient interventions. Thus, this study aimed to analyze the temporal trend of ATL cases in the state of Piauí between 2007 and 2022. **Methods:** this is a quantitative and retrospective study, carried out using secondary data on ATL cases notified in the Notifiable Diseases Information System (SINAN)/Ministry of Health/Department of Health and Environmental Surveillance, available in DATASUS. The variables analyzed were year/month of notification, municipality of residence and notification, education, race, sex, age, confirmation criteria, evolution, clinical form and type of entry. **Results:** 1,407 cases were notified in the state, with an incidence of 3.88 and 2.75 at the beginning and end of the period. There was a predominance of males (61.42%), aged between 40 and 59 years old (33.12%), incomplete elementary school (54.86%) and race/skin color brown (69,08%). The cutaneous form was predominant (90.3%), with 59.4% of cases having a clinical-laboratory diagnosis. Of the total, 58.1% cases progressed to cure. **Conclusion:** ATL has emerged as a frequently notified condition, posing a significant challenge to local public health, affecting a specific social profile that requires actions at different levels of care, with a positive impact on the prevention and control of the disease in the state.

Keywords: *Neglected Diseases. Health Information Systems. Epidemiological Time Series Studies. Compulsory Notification. Epidemiological Monitoring.*

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RESUMO

Justificativa e Objetivos: a leishmaniose tegumentar americana (LTA) é um problema de saúde pública, e seu controle persiste um desafio em territórios com expressiva vulnerabilidade social. O Piauí é um dos estados do Brasil mais vulneráveis socialmente, e conhecer o perfil das notificações pode servir de apoio na implementação de intervenções mais eficientes. Assim, este trabalho teve como objetivo analisar a tendência temporal dos casos de LTA no estado do Piauí entre os anos de 2007 e 2022. **Métodos:** trata-se de estudo quantitativo e retrospectivo, realizado a partir de dados secundários, de casos de LTA, notificados no Sistema de Informação de Agravos de Notificação (SINAN)/Ministério da Saúde/Secretaria de Vigilância em Saúde e Ambiente, disponibilizados no DATASUS. As variáveis analisadas foram ano/mês de notificação, município de residência e de notificação, escolaridade, raça, sexo, idade, critérios de confirmação, evolução, forma clínica e tipo de entrada. **Resultados:** foram notificados 1.407 casos no estado, com incidência de 3,88 e 2,75 no início e fim do período. Houve predominância do sexo masculino (61,42%), idade entre 40 e 59 anos (33,12%), ensino fundamental incompleto (54,86%) e raça/cor parda (69,08%). A forma cutânea foi predominante (90,3%), com 59,4% dos casos com diagnóstico clínico-laboratorial. Do total, 58,1% casos evoluíram para cura. **Conclusão:** a LTA emergiu como uma condição frequentemente notificada, configurando-se um desafio significativo para a saúde pública local, atingindo um perfil social específico que necessita de ações nos diversos níveis de atenção, com impacto positivo na prevenção e controle da doença no estado.

Descritores: *Doenças Negligenciadas. Sistemas de Informação em Saúde. Estudos de Séries Temporais. Notificação Compulsória. Vigilância Epidemiológica.*

RESUMEN

Justificación y Objetivos: la leishmaniasis cutánea americana (LCA) es un problema de salud **pública y** su control sigue siendo un desafío en territorios con importante vulnerabilidad social. Piauí es uno de los estados socialmente más vulnerables de Brasil, y conocer el perfil de las notificaciones puede apoyar la implementación de intervenciones más eficientes. Por tanto, este trabajo tuvo como objetivo analizar la tendencia temporal de los casos de LCA en el estado de Piauí entre los años 2007 y 2022. **Métodos:** se trata de un estudio cuantitativo y retrospectivo, realizado a partir de datos secundarios, de casos de LCA, reportados en el Sistema de Información de Enfermedades de Declaración Obligatoria (SINAN)/Ministerio de Salud/Secretaría de Vigilancia de Salud y Ambiente, disponible en DATASUS. Las variables analizadas fueron año/mes de notificación, municipio de residencia y notificación, escolaridad, raza, sexo, edad, criterios de confirmación, evolución, forma clínica y tipo de ingreso. **Resultados:** se reportaron 1,407 casos en el estado, con una incidencia de 3.88 y 2.75 al inicio y al final del período. Hubo predominio del sexo masculino (61,42%), con edades entre 40 y 59 años (33,12%), educación primaria incompleta (54,86%) y color de piel/raza parda (69,08%). La forma cutánea fue predominante (90,3%), teniendo el 59,4% de los casos diagnóstico clínico-laboratorio. Del total, el 58,1% de los casos progresaron hasta la curación. **Conclusión:** la LTA ha surgido como una patología reportada con frecuencia, planteando un importante desafío para la salud pública local, alcanzando un perfil social específico que requiere acciones en los diferentes niveles de atención, con un impacto positivo en la prevención y control de la enfermedad en el estado.

Palabras Clave: *Enfermedades Desatendidas. Sistemas de Información en Salud. Estudios de Series Temporales Epidemiológicas. Notificación Obligatoria. Vigilancia Epidemiológica.*

INTRODUCTION

Neglected tropical diseases are a diverse group of diseases caused by protozoa, helminths, parasites, bacteria, viruses, and fungi. It is estimated that two billion people are at risk of acquiring these diseases, primarily due to their prevalence in tropical and subtropical regions of Asia, Africa, and the Americas. These diseases predominantly affect impoverished and underserved populations with limited access to basic sanitation, clean water, and healthcare services.[1,2]

American tegumentary leishmaniasis (ATL) is a zoonotic disease with mandatory notification. It typically presents in two common clinical forms: cutaneous (CL) and mucocutaneous (MCL). ATL is non-contagious and has a low mortality rate. It is caused by several species of intracellular protozoa from the *Leishmania* genus and is transmitted by the bite of infected female sandflies belonging to the *Diptera* order, specifically the *Lutzomyia* genus. In Brazil, there are seven pathogenic species responsible for the disease, with *L. (Viannia) guyanensis*, *L. (V.) braziliensis*, and *L. (Leishmania) amazonensis* being the most prominent.[3–5] The cutaneous form of ATL is characterized by papular lesions that develop into nodules and ulcers at the insect bite sites. In contrast, the mucosal or mucocutaneous form of ATL involves progressive damage to the oral, nasal, and pharyngeal cavities.[6,7]

According to the Pan American Health Organization (PAHO),[1] ATL occurs in 21 South American countries, being endemic in 19 of them, with cases concentrated mainly in Brazil, Colombia, and Peru. From 2001 to 2021, 17 countries in the region notified more than one million cases of cutaneous ATL, with the mucosal form affecting an average of over 50,000 people per year.[1] In Brazil, particularly in the state of Piauí, more than 800 cases were

notified between 2007 and 2017.[8,9]

ATL is primarily diagnosed based on clinical characteristics, with various available methods differing in accuracy and availability in healthcare services. Key diagnostic methods include parasitological, molecular, and immunological tests. A clinical diagnosis can be established through a detailed medical history and physical examination, focusing on cutaneous and mucosal lesions.[10]

Treatment for cutaneous leishmaniasis typically involves pentavalent antimonials; however, depending on the identified species, other effective medications like miltefosine may be used, especially for infections caused by *L. guyanensis* and *L. panamensis*. For mucocutaneous leishmaniasis, while antimonials have low evidence, they are strongly recommended. They can also be combined with pentoxifylline, amphotericin B, or miltefosine in cases of therapeutic failure or special circumstances.[11]

In general, neglected diseases are the target of specific actions aimed at gradually reducing their prevalence worldwide, with a strong association with modern epidemiological categories such as poverty and the marginalization of populations in at-risk areas.[2] Leishmaniasis follows this same pattern, posing a significant challenge in regions or territories with high social vulnerability, such as Brazil. There is a direct relationship between its occurrence and the Human Development Index.

This study is justified by the importance of understanding the notification profile and the distribution of cases in a region to support the implementation of more effective interventions as well as guiding public policies for controlling and preventing the disease in the state. Therefore, this work aimed to analyze the temporal trend of ATL cases in the state of Piauí from 2007 to 2022.

METHODS

This is a quantitative and retrospective study aimed at analyzing the time series of notified ATL cases in Piauí between 2007 and 2022. Data were collected in December 2023 from the Information System for Notifiable Diseases (SINAN - *Sistema de Informação de Agravos de Notificação*) of the Unified Health System Department of Informatics (DATASUS - *Departamento de Informática do Sistema Único de Saúde*).

Piauí, located in northeastern Brazil, lies between 2°44'49" and 10°55'05", south latitude, and 40°22'12" and 45°59'42", west longitude. It comprises 224 municipalities and covers an area of 251,611,929 km^2. The state is divided into four mesoregions, such as North, Center-North, Southeast, and Southwest. The region has a semi-arid climate, characterized by long dry periods and regular rainfall at the beginning of the year, with precipitation ranging from 600 mm to 1,200 mm.[12] In 2020, the population of Piauí was estimated at 3,281,480 inhabitants, resulting in a population density of 12.40 inhabitants per km^2.[13]

The platform was used with various filters applied to create a database for collecting information on different types of variables that can better characterize the prevalence of ATL in the state of Piauí. The study focused on temporal (year and month of notification), clinical (outcome, confirmation criteria, clinical form, and type of entry), geographic (municipality of notification and residence) and sociodemographic variables (age, sex, race, and education level).

In addition to presenting the absolute number of notified cases per year, the relative percentage of notified cases for each variable was measured, along with the incidence rate per 100,000 inhabitants for the state population and the capital, Teresina. For municipalities with fewer than 100,000 inhabitants, the incidence rate was calculated per 10,000 inhabitants using the formula: (number of notified cases / population) X 100,000 or 10,000.

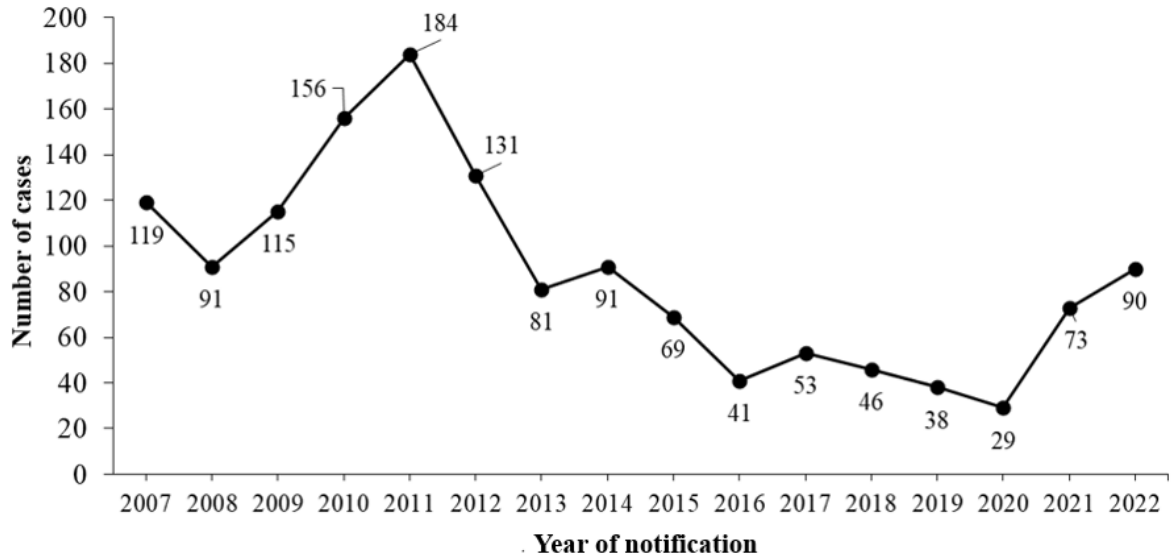
Comparisons between categories within variables were used to identify statistical differences, primarily related to the municipality of notification, year of notification, age group, and education level. For a population of 10,000 inhabitants, contingency tables were constructed, and Pearson's chi-square test was performed with a significance level of $P<0.05$.

This study was exempted from assessment by Research Ethics Committee, as it involved the analysis of public domain data, where it was not possible to identify individuals.[14]

RESULTS

From 2007 to 2022, 1,407 cases were notified. Observing ATL notifications over these years, the highest peak occurred between 2007 and 2012, ranging from 91 cases in 2008 to the highest record of 184 cases in 2011, representing an approximate twofold increase in ATL notifications. There is a significant downward trend when comparing 2007-2011 ($\chi 2=103.2$; $P<0.005$). After 2011, a decrease and subsequent stability was observed, with fewer than 100 cases recorded, and 2020 marked the lowest number (29 cases). However, from 2020 onwards, there is a trend of increasing cases, with 90 cases notified in 2022, the last year presented in this study (Figure 1).

The majority of cases were of the cutaneous clinical form (90.3%). The clinical-laboratory criterion was the predominant method (60.7%) and was used in the diagnosis of 756 cutaneous cases (53.7%) and 90 mucosal cases (6.4%). The entry type for patients with different clinical manifestations of ATL was above 80% for new cases, with a relapse rate of 5.5%. The progression of these cases was positive, with cure being the most prevalent outcome, accounting for more than 50% of notified cases. Other variables, such as abandonment and change of diagnosis, occurred with low frequency (below 3%), and death due to the disease accounted for only 0.1% of the total notified cases (Table 1)



Source: Ministry of Health/SVSA - Notifiable Diseases Information System - SINAN (DATASUS).

Figure 1. Time series of notified cases in the state of Piauí from 2007 to 2022.

Table 1. Distribution of American tegumentary leishmaniasis cases according to the diagnosed clinical form, highlighting the confirmation criteria, entry type, and progression of notified cases in the state of Piauí (2007-2022).

Confirmation criterion	Ign./blank	%	Cutaneous	%	Mucosal	%	Total	%
Clinical-laboratory	8	0.6	756	53.7	90	6.4	854	60.7
Clinical-epidemiological	2	0.1	515	36.6	36	2.6	553	39.3
Entry type								
Ign./blank	10	0.7	34	2.4	5	0.4	49	3.5
New case	-	-	1.170	83.2	111	7.9	1,281	91
Relapse	-	-	67	4.8	10	0.7	77	5.5
Progression								
Ign./blank	6	0.4	434	30.8	53	3.8	493	35
Cure	3	0.2	749	53.2	66	4.7	818	58.1
Abandonment	1	0.1	14	1	-	-	15	1.1
Death due to American cutaneous leishmaniasis	-	-	1	0.1	1	0.1	2	0.1
Death due to another cause	-	-	1	0.4	1	0.1	6	0.4
Transfer	-	-	3	2.7	3	0.2	41	2.9
Change of diagnosis	-	-	2	2.1	2	0.1	32	2.3

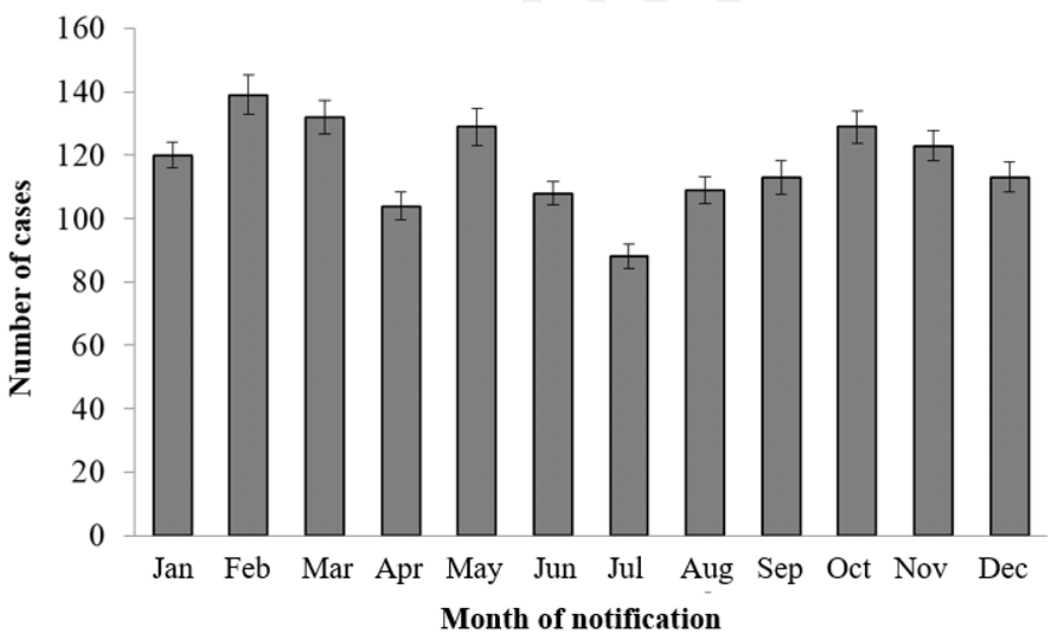
Source: Ministry of Health/SVSA - Notifiable Diseases Information System - SINAN (DATASUS). Abbreviations: Ign.: Ignored

The incidence of ATL in the state during the historical series was 42.87/100,000 inhabitants. There was a shift in the ranking between the municipalities that notified cases and the municipalities of residence of patients. The differences were concentrated in the municipalities of Inhuma, Barras, Ipiranga, and Palmeira. In the capital, Teresina, 677 cases were notified (48.1%), and, when compared to other municipalities, it concentrated the highest number of cases, with a significant difference ($\chi 2=95.4$; $P<0.05$). The city of Ipiranga Piauí had the lowest prevalence of notified cases, with 19 patients (1.4%). The same pattern was observed in the data related to the municipality of residence, with 396 cases (28.1%) from Teresina, with an incidence rate of 45.61/100,000 inhabitants. While the incidence rates in other municipalities were elevated due to their smaller populations (<100,000 inhabitants), the city of Altos had the highest incidence rate, at 45.31/10,000 inhabitants (Table 2).

Table 2. Ranking of municipalities that notified American tegumentary leishmaniasis cases and municipalities of residence of patients affected by American tegumentary leishmaniasis in the state of Piauí (2007-2022).

N	Municipality of notification	Total	%	Municipality of residence	Total	%	Inc
1	Teresina	677	48.1	Teresina*	396	28.1	45.61*
2	Altos	161	11.4	Altos	184	13.1	45.31
3	Pedro II	72	5.1	Pedro II	85	6	21.91
4	Luzilândia	31	2.2	Luzilândia	31	2.2	12.15
5	Uruçuí	29	2.1	Uruçuí	31	2.2	12.3
6	Inhuma	26	1.8	Barras	30	2.1	6.35
7	Palmeira Piauí	23	1.6	Ipiranga do Piauí	29	2.1	29.47
8	Ipiranga do Piauí	19	1.4	Inhuma	28	2	18.27

Source: Ministry of Health/SVSA - Notifiable Diseases Information System - SINAN (DATASUS).
**In Teresina, since it has more than 100,000 inhabitants, the incidence was proportional to the population (100,000 inhabitants), and in other cities, the incidence used was based on 10,000 inhabitants.*



Source: Ministry of Health/SVSA - Notifiable Diseases Information System - SINAN (DATASUS).

Figure 2. Number of American tegumentary leishmaniasis cases notified per month in the state of Piauí during the historical series from 2007 to 2022.

The monthly reporting of ATL did not show significant variations. In the analysis, more than 80 cases were notified each month, with the highest number in February and the lowest in July (Figure 2).

According to sociodemographic variables, males were the most affected group, with 858 diagnosed cases (61.42%). Regarding age groups, the highest number of reports was among adults aged 40 to 59 years, with an average of 466 cases (33.12%), making this the highest-risk group for infection. The notification of ATL among adults aged 20 to 59 years (the group with the highest prevalence) was different when compared to adults over 60 years of age ($\chi 2=272.15$; $P<0.005$). Finally, regarding educational level, patients affected by ATL predominantly had a low level of education. Moreover, 54.86% of affected patients had some level of incomplete elementary school (Table 3).

Table 3. Sociodemographic variables of confirmed American tegumentary leishmaniasis cases in residents of the state of Piauí from 2007 to 2022 according to sex, age group, and race/skin color.

Variables	Total	%
Sex		
Woman	544	38.66
Man	863	61.34
Age group		
< 1 year	15	1.07
1 – 9	49	3.48
10 – 14	66	4.69
15 – 19	68	4.83
20 – 39	417	29.64
40 – 59	466	33.12
60 – 69	182	12.94
70 – 79	94	6.68
> 80 years	50	3.55
Educational level		
Ign./blank	195	13.86
Illiterate	140	9.95
Incomplete 1st to 4th grade of elementary school	272	19.33
Complete 4th grade of elementary school	150	10.66
Incomplete 5th to 8th grade of elementary school	216	16.35
Complete elementary school	157	11.16
Incomplete high school	78	5.54
Complete high school	92	6.54
Incomplete higher education	19	1.35
Complete higher education	39	2.77
Not applicable	49	3.48
Race/skin color		
Yellow	11	0.78
White	253	17.98
Indigenous	4	0.28
Brown	972	69.08
Black	132	9.38

Source: Ministry of Health/SVSA - Notifiable Diseases Information System - SINAN (DATASUS). Abbreviations: Ign: ignored.

DISCUSSION

The present study provides a broader perspective and diagnosis of ATL, highlighting various epidemiological and statistical variables according to clinical manifestations, municipalities with the highest number of notifications, municipalities of residence, and the sociodemographic and temporal status of the disease. As a disease of global public health concern, ATL exhibits diversity in clinical and epidemiological aspects.

Brazil is among the ten countries with the highest number of notified ATL cases worldwide, with 39% of the cases concentrated in the northeast region, making it a focal point for investigating the disease's dynamics. In the state of Piauí, ATL is particularly significant due to the consistent reporting of this condition relative to the size of its population and territory.[1,15]

When examining monthly notifications, no consistent pattern emerged regarding the month with the highest number of reports, indicating that ATL is a recurrently notified disease throughout the year, unlike other vector-borne diseases. In the case of leishmaniasis, despite the fluctuation of insect populations associated with seasonal changes, with an increase in insects after rainy periods, ATL did not follow this transmission pattern. This may be related to the fact that ATL involves dermatological alterations, where the appearance of lesions may take longer for symptoms to manifest.[16]

An increase in notifications was observed in more populous cities compared to rural areas. The pattern of leishmaniasis occurrence in cities changed over the years, with a higher number of cases in more populous cities in the state. This trend could also be influenced by residents traveling to other municipalities in search of better healthcare services and by the disease's expansion into urban areas. This phenomenon has also been observed in other states in the northeast region.[4,16,17] The high rate of urbanization, loss of natural habitats for insect vectors, human interference in natural habitats, and migratory processes are factors that have contributed to the spread of the disease.[15]

Sociodemographic variables highlight the social groups most affected by ATL, characterized by low-income populations with low educational levels and limited access to disease prevention and control services. Despite the low mortality rate, ATL is considered one of the most concerning dermatological conditions in Brazil due to sequels it causes in patients, including body deformities and mucosal region involvement through hard-to-heal lesions if not properly treated. These issues have a significant psychological impact on patients, leading to stigmas with social and economic consequences, as ATL can be considered an occupational disease.[17,18]

It is important to characterize the social groups most affected for the benefit of the scientific community and health authorities. In this study, the adult population was most affected, with a notable predominance among male patients, those of brown race/color, and individuals with incomplete elementary or high school, similar to results found in other states in the northeast.[4,19,20]. This at-risk group is primarily related to economically active and working individuals. ATL, with its occupational nature, involves jobs in activities such as resource extraction, exposure to forested areas, construction, animal husbandry, residences near forests, and other rural activities.[4,17]

Among the notified cases, the majority progressed to cure, with a low number of deaths, showing good overall case progression. However, more than 30% of cases were notified as "ignored/blank" possibly due to a lack of information about patients after the initial diagnosis. Additionally, the study explored the entry type for patients, with a relapse rate of 5.5% of cases, highlighting the need for health action networks to focus on improving follow-up measures, such as active case finding in endemic areas and health education, to prevent reinfection that could worsen the clinical condition and hinder recovery.[21]

Another relevant finding is the change in diagnosis presented in this study. Although occurring in approximately 2.3% of cases, it is often confused with other diseases that present similar clinical manifestations (body lesions), which may lead to underreporting of ATL. In such cases, the disease may be misdiagnosed and treated as another condition. Therefore, clinical-laboratory diagnosis is the most appropriate, requiring suitable methods for confirmation, especially due to potential confusion with other diseases.[22]

Conversely, the study acknowledges the limitations caused by the high prevalence of cases notified as "ignored/blank" due to the lack of patient follow-up after the initial diagnosis. This gap could make the studied profile more reliable and valuable for public policy development. Nevertheless, the study highlights significant improvements in the quality of information, with easier access and better presentation of results on the platform.

In conclusion, this study contributes to understanding risk areas, clinical aspects, and vulnerable groups, enhancing scientific knowledge and dissemination for disease prevention and control in the state. Addressing stigmas related to lesions, proper treatment, and effective diagnosis can lead to reduced recurrences and new cases. Additionally, expanding awareness and sensitization campaigns by health education teams in various settings is crucial, considering the need to understand ATL in the occupational context, particularly when there is exposure to risk areas and the vector insect during work activities.

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AUTHORS' CONTRIBUTIONS

Daniela Soares Leite contributed to the bibliographical research, translations, writing of the summary, introduction, discussion, interpretation and description of results, conclusions and review. **Jamileh Marinho de Carvalho** contributed to the bibliographical research, translations, writing of the summary, introduction, discussion, interpretation and description of results, conclusions and review. **Maura de Souza Pereira Portilho** contributed to the bibliographical research, writing of results, discussion, interpretation, conclusions, review and statistics. **Marcela Bezerra Dias** contributed to writing the results, interpreting the results, conclusions, review and statistics. **Kleberson de Oliveira** contributed to the writing of the methodology, review, interpretation and description of the results and conclusions. **Henrique Rafael Pontes Ferreira** contributed to the bibliographical research, writing the summary, introduction, methodology, discussion, interpretation and description of results, conclusions, review and statistics.

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

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ORIGINAL ARTICLE

Demographic and clinical factors associated with hospital infections in burned children and adolescents

Fatores demográficos e clínicos associados às infecções hospitalares em crianças e adolescentes vítimas de queimaduras

Factores demográficos y clínicos asociados a las infecciones hospitalarias en niños y adolescentes víctimas de quemaduras

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Corresponding Author:
Susany Franciely Pimenta
susany.franciely@uel.br

Address: Sidrac Silva Filho nº 175, apto 262, bloco 2, Jardim Santiago, Londrina, Paraná, Brasil.

Susany Franciely Pimenta[1];
Elisângela Flauzino Zampar[1];
Ana Paula Contiero[2];
Flávia Meneguetti Pieri[1];
Jaqueline Dario Capobiango[1];
Rosângela Aparecida Pimenta[1];

[1] *Universidade Estadual de Londrina, Londrina, Paraná, Brazil.*
[2] *Universidade Estadual do Oeste do Paraná (UNIOESTE), Foz do Iguaçu- CELS, Paraná, Brasil.*

ABSTRACT

Background and Objectives: burns are a leading cause of domestic accidents and the third leading cause of mortality in children and adolescents under 14 years old. This study aimed to identify demographic and clinical factors associated with healthcare-associated infections (HAIs) in burn victims under 18 years old treated at a Burn Treatment Center (BTC). **Methods:** this cross-sectional analytical study was conducted at the BTC of a public hospital using HAI notification records and medical records of patients under 18 years hospitalized from 2009 to 2019. The demographic variables considered were sex and age, while the clinical variables included causal agent, total body surface area (TBSA), burn depth, duration and location of hospitalization, dates of admission and infection detection, diagnosis of HAIs, invasive and surgical procedures, site of infection, etiological agent, antimicrobial susceptibility profile, antimicrobial agents used in the treatment of infections, diagnosis of sepsis and septic shock as well as the clinical outcome. Absolute and relative frequencies were used, and the chi-square test was applied for categorical variables. Multivariate analysis was conducted using Poisson regression with robust variance adjustment. **Results:** among the 591 victims, 187 (31.6%) developed HAIs. HAIs were associated with larger TBSA, third-degree burns, longer hospitalization, and mortality. Factors associated with HAIs included burn area ≥21%, hospitalization ≥15 days, and mortality. The prevalent microorganisms were multidrug-resistant (MDR) *Acinetobacter baumannii* and MDR *Pseudomonas aeruginosa*. **Conclusion:** children with severe burns and prolonged hospitalization were more vulnerable to HAIs and associated mortality.

Keywords: *Child. Adolescent. Burns. Nosocomial Infection.*

RESUMO

Justificativa e Objetivos: as queimaduras são uma das principais causas de acidentes domésticos e a terceira principal causa de mortalidade em crianças e adolescentes menores de 14 anos. O objetivo deste estudo é identificar os fatores demográficos e clínicos associados às infecções relacionadas à assistência à saúde (IRAS) em vítimas de queimaduras menores de 18 anos atendidas no Centro de Tratamento de Queimados (CTQ). **Métodos:** estudo transversal analítico, realizado no CTQ de um hospital público, utilizando fichas de notificação de IRAS e prontuários de pacientes menores de 18 anos hospitalizados de 2009 a 2019. As variáveis demográficas consideradas foram sexo e idade, enquanto as variáveis clínicas incluíram agente causal, superfície corporal queimada (SCQ), profundidade da queimadura, tempo e local de hospitalização, datas de admissão e de detecção da infecção, diagnóstico de IRAS, procedimentos invasivos e cirúrgicos, sítio da infecção, agente etiológico, perfil de sensibilidade aos antimicrobianos, antimicrobianos utilizados no tratamento das infecções, diagnóstico de sepse e choque séptico, além do desfecho clínico. Foram utilizadas frequências absolutas e relativas, e o teste qui-quadrado foi usado para variáveis categóricas. A análise multivariada foi conduzida por regressão de Poisson com ajuste de variância robusta. **Resultados:** entre as 591 vítimas, 187 (31,6%) desenvolveram IRAS. As IRAS foram associadas a maior SCQ, queimaduras de 3° grau, maior tempo de hospitalização e óbito. Fatores associados às IRAS incluíram área queimada ≥21%, tempo de hospitalização ≥15 dias e óbito. Microrganismos prevalentes foram *Acinetobacter baumannii* multirresistente (MR) e *Pseudomonas aeruginosa* MR. **Conclusão:** crianças com queimaduras graves e prolongada hospitalização apresentaram maior vulnerabilidade às IRAS e óbitos associados.

Descritores: *Criança. Adolescente. Queimaduras. Infecção Hospitalar.*

RESUMEN

Justificación y Objetivos: las quemaduras son una de las principales causas de accidentes domésticos y la tercera causa principal de mortalidad en niños y adolescentes menores de 14 años. Este estudio tiene como objetivo identificar los factores demográficos y clínicos asociados a las infecciones relacionadas con la asistencia sanitaria (IRAS) en víctimas de quemaduras menores de 18 años atendidas en el Centro de Tratamiento de Quemaduras (CTQ). **Métodos:** estudio transversal analítico, realizado en el CTQ de un hospital público utilizando registros de notificación de IRAS y prontuarios de pacientes menores de 18 años hospitalizados de 2009 a 2019. Las variables demográficas consideradas fueron sexo y edad, mientras que las variables clínicas incluyeron agente causal, superficie corporal quemada (SCQ), profundidad de la quemadura, tiempo y lugar de hospitalización, fechas de admisión y detección de la infección, diagnóstico de IRAS, procedimientos invasivos y quirúrgicos, sitio de la infección, agente etiológico, perfil de sensibilidad a los antimicrobianos, antimicrobianos utilizados en el tratamiento de las infecciones, diagnóstico de sepsis y shock séptico, además del desenlace clínico. Se utilizaron frecuencias absolutas y relativas, y se aplicó la prueba chi-cuadrado para variables categóricas. El análisis multivariado se realizó mediante regresión de Poisson con ajuste de varianza robusto. **Resultados:** de las 591 víctimas, 187 (31,6%) desarrollaron IRAS. Las IRAS se asociaron con una mayor SCQ, quemaduras de tercer grado, mayor tiempo de hospitalización y mortalidad. Los factores asociados a las IRAS incluyeron área quemada ≥21%, tiempo de hospitalización ≥15 días y mortalidad. Los microorganismos prevalentes fueron *Acinetobacter baumannii* multirresistente (MR) y *Pseudomonas aeruginosa* MR. **Conclusión:** los niños con quemaduras graves y hospitalización prolongada presentaron una mayor vulnerabilidad a las IRAS y a la mortalidad asociada.

Palabras Clave: *Ninõ. Adolescente. Quemaduras. Infección Hospitalaria.*

INTRODUCTION

Burns are one of the main causes of domestic accidents, and represent the third leading cause of mortality in children and adolescents under 14 years of age.[1,2,3] With a global estimate of 180,000 deaths annually, the impact of burns on public health is significant.[4] In Brazil, the Brazilian Burn Society reports around 1 million cases annually, with 2,500 deaths, resulting directly from burns or from complications such as infections, sepsis or organ failure.[5]

Children and adolescents are particularly vulnerable to burns, due to their age-related characteristics of being observant and curious, which exposes them to high risks.[1,2] Furthermore, the fragility of the developing immune system and long hospitalization contribute to the proliferation of resistant microorganisms, complicating clinical picture and prolonging recovery.[5-7]

Some factors favor the development of secondary infections, including the skin and mucosa integrity breakdown, which leads to a loss of the barrier against microorganisms; increased capillary permeability, which facilitates the migration of microorganisms and toxins into the bloodstream; and immunosuppression associated with trauma.[6,7] Burn patients are exposed to invasive and surgical procedures and prolonged hospitalization, increasing the risk of healthcare-associated infections (HAIs), which can occur during hospitalization or after discharge.[8-11] Although there are studies on the vulne-

rability of children and adolescents to burns and their complications, the publication adds value to the existing literature by offering a detailed and specific analysis on HAIs in this age group.[5,7,12] Understanding these aspects better is essential to develop more effective prevention and treatment strategies, aiming to reduce mortality associated with burns and infections in these vulnerable groups.[12] Therefore, the present study aims to identify the demographic and clinical factors associated with HAIs in burn victims under 18 years of age treated at the Burn Treatment Center (BTC).

METHODS

This is an analytical cross-sectional study conducted at the BTC of a public university hospital that is a reference for the northern region of Paraná and other neighboring states. The BTC was opened in 2007 and currently has ten ward beds, eight beds in the Burn Treatment Unit (BTU), an Emergency Room, two surgical rooms, a balneotherapy room, an outpatient clinic and a hyperbaric oxygen therapy room.

The study population consisted of children and adolescents under the age of 18, of both sexes, hospitalized for burns, from January 2009 to December 2019. Patients under the age of 18 hospitalized for burns in a period longer than 24 hours were included. Admissions for elective surgeries were excluded.

The classification of patients as children and adolescents was carried out in accordance with the Brazilian Child and Adolescent Statute (In Portuguese, *Estatuto da Criança e do Adolescente* - ECA), which defines children as individuals up to 12 years of age and adolescents as those aged 12 years up to 18 years.[13]

For data collection, the institution's statistics department provided records of all patients admitted to the BTC during the period of interest. The unit's spreadsheets, physical medical records and the MedvVew computerized system, which allows access to electronic medical records and laboratory tests, were also used.

Regarding the diagnosis of HAIs, this was obtained through individual forms, with the notification of HAIs filled out by the Hospital Infection Control Commission (HICC) team, which evaluates children with infectious diseases, in accordance with the International Classification of Diseases (ICD-10) and the Brazilian National Health Regulatory Agency (In Portuguese, *Agência Nacional de Vigilância Sanitária* - ANVISA) definition, in accordance with the revisions of the diagnostic criteria established by ANVISA.

It is noteworthy that information with the diagnosis of HAIs was included in accordance with the notifications of all infections associated or not with invasive devices as well as that infections were acquired during individuals' stay in the hospital and after the first 48 hours of hospitalization, associated with laboratory tests and clinical signs specific to each type. In cases where patients presented a new episode of infection associated with invasive devices, it was only considered after a period of 14 days, with the presence of new episodes of signs and symptoms and with positive laboratory test results.

For the classification of antimicrobial resistance, microorganisms were divided into two groups: multidrug-resistant (MDR), which included Gram-negative bacilli, resistant to 3rd and 4th generation cephalosporins, extended-spectrum β-lactamase (ESBL) producers and oxacillin-resistant *Staphylococcus*, and carbapenem-resistant (CR) Gram-negative bacilli.[14]

The total body surface area (TBSA) was calculated by a plastic surgeon using the Lund and Browder diagram and recorded in the admission medical record. A previously developed and tested instrument was used to collect information, containing demographic and clinical variables. Data collection took place from August to September 2020.

Information was entered into a Microsoft Excel® spreadsheet, in which demographic variables were categorized according to sex (male and female) and age (≤1 year, 2 to 6 years, ≥7 to 11 years and ≥12 to <18 years). Clinical variables were: causal agent (scald, flame and others, such as electrical, contact with heated surface and chemical); TBSA (≤10%, 11% to 24%, and ≥25%); burn depth (2nd, 3rd, or 2nd and 3rd degrees combined); length of hospital stay (≤14 days and >15 days); place of hospitalization; date of admission and infection detection; diagnosis of HAI (yes and no); invasive and surgical procedures (yes and no); infection site; etiologic agent; antimicrobial sensitivity profile; antimicrobial agents used in the treatment of infections; diagnosis of sepsis and septic shock (yes and no); and outcome (discharge or death). Subsequently, the IBM Statistical Package for the Social Sciences (SPSS) version 20.0® was used for statistical analysis, taking into account the significance level of $p<0.05$.

In descriptive analysis, absolute and relative frequencies were used for the variables sex, age group, TBSA, burn depth, length of hospital stay, outcome, invasive procedures, surgical procedures, HAIs and complications. To verify the difference between categorical variables, the chi-square test was (x^2) was applied. In multivariate analysis, Prevalence Ratios (PR) and their respective 95% Confidence Intervals (95% CI) were calculated using Poisson regression, with robust variance adjustment. This regression model allows us to evaluate the relationship between qualitative factors and a binary response variable.

Collinearity diagnosis was performed to determine whether the variables were correlated. When constructing the multivariate model, the crossover of the predictor variables sex, age group, TBSA, burn depth, causal agent (scald, flame and others), length of hospitalization (≤14 days and >15 days) and outcome (discharge and death) with the response variable presented HAI (yes or no) was considered. After multivariate analysis, the backward method was used, which removes, one by one, the factors with a p-value >0.20 from the model, with the aim of controlling confounding factors. Thus, the final adjusted model was composed of these predictor variables: TBSA; burn depth; length of hospital stay; and outcome discharge or death. In all stages, model adjustment tests

were applied (Omnibus test, model effects test and Akaike Information Criteria (AIC)).

This study is an excerpt from the research project entitled *"Avaliação das Infecções Relacionadas à Assistência à Saúde em Crianças e Adolescentes"*, and complied with the ethical precepts established by the Ministry of Health (Brazilian National Health Council Resolutions 466/2012, 510/2016 and 580/2018), authorized by the hospital management and approved by the institution's Research Ethics Committee on July 21, 2020, under Opinion 4,165,597, with Certificate of Approval for Ethical Consideration (In Portuguese, *Certificado de Aprovação para Apreciação Ética* - CAAE) 28-68119.6.0000.5231.

RESULTS

During the study period, 591 children and adolescents under 18 years of age were hospitalized due to burns, of which 187 (31.6%) developed HAIs. The analysis of victims who acquired HAIs showed similarity between sexes and age group, without statistical significance. However, the age group of 2 to 6 years was the most prevalent in burn accidents. Children and adolescents with higher TBSA (≥ 25%), 3rd degree burns, flame burns, length of hospitalization (≥ 15 days) and with death outcome had a higher percentage of HAIs, with statistical significance (Table 1).

Among the children and adolescents who developed HAIs, 127 (67.9%) required intensive care for a period of stay that varied from one to 119 days and a median of ten days.

Those with a larger TBSA area, longer hospital stay and death were significantly associated with HAIs. Second- and third-degree burns proved to be a protective factor when compared to third-degree burns. Data analysis suggests a higher frequency of second-degree burns compared to third-degree burns (Table 2).

Table 3 describes the distribution of procedures performed in individuals with HAI. Central catheter insertion was the most common procedure (28.8%), followed by surgeries with two or more debridement (48.1%).

Some children and adolescents had more than one infection (1.72%), totaling 321 infections, with a predominance of skin and soft tissue infection (SSTI) (31.2%) and ventilator-associated pneumonia (VAP) (30.8%). It is noteworthy that 64.7% of the population developed sepsis.

Among the laboratory results, 196 positive cultures were found with 114 isolated microorganisms, of which 73 demonstrated resistance to antimicrobial agents. Gram-negative bacilli were predominant

Table 1. Distribution of demographic and clinical variables of children under 18 years of age hospitalized for burns and who developed healthcare-associated infection. Londrina, Paraná, Brazil, 2009-2019.

Variables	Total (n=591)		HAIS		p-value[a]
	N	%	Yes (n=187) n (%)	No (n=404) n (%)	
Sex					
Male	390	66	120 (30.8)	270 (68.2)	0.293
Female	201	34	67 (33.3)	134 (66.7)	
Age group					
≤1 year	28	4.7	8 (28.6)	20 (71.4)	0.802
2 a 6 years	322	54.5	100 (31.1)	222 (68.9)	
≥7 to 11 years	116	19.6	41 (35.3)	75 (64.7)	
≥12 to <18 years	125	21.2	38 (30.4)	87 (69.6)	
TBSA*					
≤10%	322	54.5	38 (11.8)	284 (88.2)	< 0.001
11% to 24%	195	33	91 (46.7)	104 (53.3)	
≥25%	74	12.5	58 (78.4)	16 (21.6)	
Burn depth					
2nd degree	139	23.5	58 (41.7)	81 (58.3)	< 0.001
2nd and 3rd degrees	354	59.9	55 (15.5)	299 (84.5)	
3rd degree	98	16.6	74 (75.5)	24 (24.5)	
Causal agent					
Scald	327	55.3	88 (26.9)	239 (73.1)	< 0.001
Flame	219	37.1	93 (42.5)	126 (57.5)	
Others**	45	7.6	6 (13.3)	39 (86.7)	
Length of hospitalization					
≤ 14 days	369	62.4	50 (13.6)	319 (86.4)	< 0.001
> 15 days	222	37.6	137 (61.7)	85 (38.3)	
Outcome					
Discharge	570	96.4	171 (30.0)	399 (70.0)	< 0.001
Death	21	3.6	16 (76.2)	5 (23.8)	

*Source: the authors (2021). Note: [a]chi-square test; *burned body surface; **others: electrical, contact with heated surface and chemical.*

Table 2. Adjusted multivariate analysis of variables regarding clinical aspects associated with healthcare-associated infection (n=187) according to a robust Poisson regression model. Londrina, Paraná, Brazil, 2009-2019.

Variables	PR[a]	95% CI[b]	P-value[c]
Total body surface area			
≥ 25%	2.47	1.75 – 3.57	<0.001
11% to 24%	2.26	1.60 – 3.19	<0.001
≤ 10%	2.00	–	–
Burn degree			
3rd degree	1.16	0.93 – 1.45	0.001
2nd and 3rd degrees	0.48	0.36 – 0.64	<0.001
2nd	1.00	–	–
Length of hospitalization			
>15 days	2.58	1.90 – 3.48	<0.001
≤14 days	1.00	–	–
Outcome			
Death	1.36	1.02 – 1.80	0.003
Discharge	1.00	–	–

Source: the author (2021). Note: [a]adjusted prevalence ratio; [b]Confidence Interval; [c]p-value for Poisson regression with robust variance.

Table 3. Distribution of invasive and surgical procedures in children and adolescents who were victims of burns and had healthcare-associated infections (n=187). Londrina, Paraná, Brazil, 2009-2019.

Variables	Total n (%)
Invasive procedures	
Central catheter	158 (28.8)
Indwelling bladder catheter	133 (24.2)
Peripheral catheter	129 (23.5)
Mechanical ventilator	129 (23.5)
Surgical procedures	
Number of debridement	
1 debridement	89 (47.6)
2 or more debridement	90 (48.1)
No indication	8 (4.3)
Number of grafts	
1 graft	78 (41.7)
2 or more grafts	49 (26.2)
No indication	60 (32.1)
Associated infections*	
Skin and soft tissue infection	100 (31.2)
Ventilator-associated pneumonia	99 (30.8)
Catheter-associated urinary tract infections	41 (12.8)
Catheter-associated bloodstream infection	32 (9.9)
Pneumonia	26 (8.1)
Bloodstream infection	23 (7.2)
Complications	
Sepsis	
Yes	121 (64.7)
No	66 (35.3)
Septic shock	
Yes	25 (20.7)
No	96 (79.3)

Source: the author (2021). Note: [a]adjusted prevalence ratio; [b]Confidence Interval; [c]p-value for Poisson regression with robust variance.

(70.9%), including MDR (30.7%) and CR (9.6%) *Acinetobacter baumannii*, in addition to MDR (16.6%) and (14.0%) CR *Pseudomonas aeruginosa*. Gram-positive bacilli accounted for 22.1% of the total, with coagulase-negative *Staphylococcus* (7.0%) and methicillin-resistant *Staphylococcus aureus* (MRSA) (4.4%) standing out. Fungal infections were observed in 7.0% of cases. A total of 693 antimicrobial agents and/or antifungals were prescribed, varying according to age group. For children under 11 years of age, the most common were amikacin sulfate and sulbactam sodium + ampicillin sodium and piperacillin + tazobactam. Adolescents received vancomycin, meropem, and tigecycline.

DISCUSSION

The difference in HAI rates between the sexes was small, suggesting that sex may not be a significant determinant of HAI risk or that other factors have a greater influence. Although the variation in HAI rates between different age groups was not significant, analysis of the demographic characteristics of the total sample indicates the relevance of additional risk factors and the need for personalized care.

A study in southern Brazil revealed a similarity in the high number of hospitalizations due to burn accidents, with 8,256 hospitalizations, with Paraná being the state with the highest rates.[3] This analysis highlights the need for preventive measures and increased surveillance to reduce the prevalence of burns in children, requiring specific care for each age group.[3]

In this study, a HAI rate of 31.6% was identified. Among patients with HAI, TBSA was higher than 25%. Flame was the most frequently identified causal agent in cases of HAI, aggravating the extent and depth of lesions. However, in the total sample, scald was the most common causal agent. These results corroborate other studies, which indicate that lesions caused by flames result in greater extent and depth of the body area, increasing susceptibility to nosocomial infection.[8,15]

Analysis revealed a strong association between TBSA and the prevalence of HAIs, with a higher risk of infections in patients with extensive burns. Children and adolescents with third-degree burns had a 1.16-fold higher prevalence of HAIs compared to those with second-degree burns.

The most frequent infections were skin and soft tissue infections, followed by VAP and urinary tract infection (UTI) associated with indwelling urinary catheters. These results are in line with systematic research that has indicated a high number of SSTIs in burn victims, representing a global problem.[12] Thermal injuries compromise tissue integrity and alter the immune system, hindering healing and increasing vulnerability to secondary infections, prolonging hospital stays.[2,8,17]

It was observed that patients hospitalized for more than 15 days had a prevalence of HAIs 2.58 times higher than patients hospitalized for 14 days or less, highlighting the impact of prolonged exposure to hospital environments on the likelihood of infections. This finding reinforces

the importance of effective infection control protocols and strategies to reduce hospital stay when appropriate.[2]

The main microorganisms found in skin infections were MDR *Pseudomonas aeruginosa, Acinetobacter baumannii* and *Staphylococcus aureus*. These data are in line with a study that highlights the vulnerability of burn victims to *Pseudomonas aeruginosa* infections.[7]

Critically ill patients, including burn patients, require continuous care and support to maintain vital functions, which may be associated with high rates of VAP. In this study, VAP was the second most prevalent infection, with the presence of pathogens such as *Acinetobacter baumannii* and *Pseudomonas aeruginosa* in tracheal secretion examinations, highlighting the vulnerability of burn patients to nosocomial infections.[16]

Children and adolescents have undergone a variety of invasive procedures, which are potential contributors to infections or complications, indicating the need for rigorous infection control practices and aseptic techniques during insertion and maintenance.[18]

In a systematic review, the authors identified that burn patients who previously used β-lactams and invasive devices had a higher risk of infections by MDR Gram-negative.[18] These findings corroborate the present study, which also observed a higher prevalence of MDR Gram-negative.[18]

Another systematic review highlighted that patients hospitalized in BTUs were at high risk of developing secondary MRSA infections, with outbreaks reported in several centers. The authors emphasized that MRSA was responsible for serious complications, such as pneumonia, sepsis, and bacteremia.[11] These results confirm the vulnerability of burn patients to nosocomial infections by MDR microorganisms, highlighting the importance of rigorous infection control measures and constant monitoring to prevent these complications.[12,18]

Regarding antimicrobial susceptibility tests, studies highlight the predominance of Gram-negative bacilli, mainly *Pseudomonas spp.* and *Acinetobacter spp.* MDR to antimicrobial agents.[9] High rates of antimicrobial resistance limit effective treatment in the population with burns, causing several complications and a major financial impact, constituting a global health problem.[7,17]

Drug resistance is occurring rapidly, especially in developing countries, due to the lack of resources for laboratory tests and medications, which hinders the choice of the appropriate drug. This situation is particularly serious in burn victims, due to exposure and immunosuppression, leading to infections and sepsis.[19] A high percentage of the population studied developed sepsis. In the literature, 75% of deaths in severe burn victims were caused by sepsis resulting from skin infections.[12,19]

The association between outcome and HAIs revealed that patients who died had a higher prevalence of HAIs compared to those who were discharged. This result reflects the severity of infectious complications and the need for intensive surveillance and early treatment to minimize infectious complications and avoid fatal outcomes.

Among the limitations of the study, the lack of specificity and underreported information in the medical records, with data obtained from secondary sources, stand out. In addition, it was not possible to access all the medical records, making it impossible to combine some clinical variables for comparison between groups.

The study revealed that children with larger TBSA area, prolonged hospitalization time and death outcome were associated with higher prevalence of HAIs. It was also found that children and adolescents underwent various invasive and surgical procedures, which represents risk factors for acquiring secondary infections, such as UTI, bloodstream infection and pneumonia. SSTI and VAP were the most prevalent HAIs, with a predominance of MDR *Acinetobacter baumannii* and *Pseudomonas aeruginosa*.

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AUTHORS' CONTRIBUTIONS

Susany Franciely Pimenta contributed to bibliographic research, writing of the abstract, introduction, methodology, discussion, interpretation and description of results, preparation of tables, conclusions, review and statistics. **Elisângela Flauzino Zampar** contributed to writing the abstract, methodology, interpretation of results, conclusions, review and statistics. **Ana Paula Contiero Toninato** contributed to writing the abstract, methodology, interpretation of results, conclusions, review and statistics. **Flávia Meneguetti Pieri** contributed to conceptualization, writing (original draft, review and statistics). **Jaqueline Dario Capobiango** contributed to project administration, writing the abstract, introduction, methodology, discussion, interpretation and description of results, conclusions, review and statistics. **Rosângela Aparecida Pimenta** contributed to project management, bibliographic research, guidance on writing the abstract, introduction, methodology, discussion, interpretation and description of results, conclusions, review and statistics.

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ORIGINAL ARTICLE

Multiple-step antimicrobial stewardship approach in a neonatal intensive care unit: a quasi-experimental study

Abordagem de controle antimicrobiano em múltiplas etapas em uma unidade de terapia intensiva neonatal: um estudo quase experimental

Enfoque de administración de antimicrobianos en múltiples etapas en una unidad de cuidados intensivos neonatales: un estudio cuasiexperimental

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Corresponding Author:
Mariana Martins Gonzaga do Nascimento
marianamgn@yahoo.com.br

Av. Antônio Carlos, 6627, Campus Pampulha,
CEP 31270-901, Belo Horizonte - MG – Brasil

Francisco Alves Farias-Filho[1];
Philipe Vieira Souza[1];
Susana Nunes da Rocha Nascimento[1];
Rafaela de Carvalho Rodrigues[2];
Mariana Martins Gonzaga do Nascimento[2];
Vinicius de Frias Carvalho[3];

[1] Pharmacy Service, Perinatal Group. Rio de Janeiro, RJ, Brazil.
[2] Faculty of Pharmacy, Federal University of Minas Gerais. Belo Horizonte, MG, Brazil.
[3] Inflammation Lab, Oswaldo Cruz Foundation, Rio de Janeiro, RJ, Brazil

ABSTRACT

Background and objectives: Antimicrobial resistance is considered one of the biggest global health challenges of the 21st century. Anti-infectives are the most frequently used medications in Neonatal Intensive Care Units, and their misuse and overuse facilitate the selection of infections caused by multidrug-resistant organisms and increase the risk of adverse effects. In this context, the aim of this study was to assess the effectiveness of a multi-step antimicrobial stewardship approach in a Neonatal Intensive Care Unit. **Methods:** This quasi-experimental longitudinal study used a pre-test/post-test design to evaluate the implementation of antimicrobial stewardship interventions delivered in four stages. In stage I, the profile of newborns was mapped. In Stage II, pharmacotherapeutic protocols for parenteral medications were developed. In Stage III, parenteral medication management for the Neonatal Intensive Care Unit was implemented. In Stage IV, an electronic dosage calculator was integrated into the Computerized Physician Order Entry. In Stage V, physicians and professionals responsible for dispensing medications were trained by clinical pharmacists. Effectiveness was assessed by comparing the incidence of prescribing errors before and after implementation. **Results:** There were 513 prescriptions during the implementation period: 332 for vancomycin, 149 for cefepime and 42 for piperacillin-tazobactam. A statistically significant reduction in the incidence of prescription errors involving dose and infusion time was observed. **Conclusion:** The implementation of multiple pharmacy-based antimicrobial stewardship interventions improved the safety profile of antimicrobial prescriptions.

Keywords: *Antimicrobial stewardship. Intensive Care Units; Neonatal. Patient Safety Medication Errors.*

RESUMO

Justificativa e objetivos: A resistência antimicrobiana é considerada um dos maiores desafios globais de saúde do século XXI. Os antimicrobianos são os medicamentos mais utilizados nas Unidades de Terapia Intensiva Neonatal

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e seu uso indevido e excessivo facilita a seleção de infecções causadas por organismos multirresistentes e aumenta o risco de efeitos adversos. Nesse contexto, o objetivo deste estudo foi avaliar a eficácia de uma abordagem de gestão antimicrobiana em múltiplas etapas em uma Unidade de Terapia Intensiva Neonatal. **Métodos:** Este estudo longitudinal quase experimental usou um desenho de pré-teste/pós-teste para avaliar a implementação de intervenções de gestão antimicrobiana realizadas em 4 etapas. Na etapa I, foi mapeado o perfil dos recém-nascidos. Na Etapa II, foram desenvolvidos protocolos farmacoterapêuticos para medicamentos parenterais. Na Etapa III, foi implementado o gerenciamento de medicamento parenteral para a Unidade de Tratamento Intensivo Neonatal. Etapa IV, uma calculadora eletrônica de dosagem foi integrada ao sistema informatizado de prescrição médica. Na Etapa V, médicos e profissionais responsáveis pela dispensação de medicamentos foram treinados por farmacêuticos clínicos. A efetividade foi avaliada comparando a incidência de erros de prescrição antes e depois da implementação. **Resultados:** Houve 513 prescrições durante o período de implantação, sendo 332 de vancomicina, 149 de cefepima e 42 de piperacilina-tazobactam. Foi observada uma redução estatisticamente significativa na incidência de erros de prescrição envolvendo dose e tempo de infusão. **Conclusão:** A implementação de múltiplas intervenções de gestão antimicrobiana baseadas em farmácias resultou numa melhoria no perfil de segurança das prescrições antimicrobianas.

Descritores: *Gestão de antimicrobianos. Unidades de Terapia Intensiva. Neonatal. Segurança do paciente. Erros de medicação.*

RESUMEN

Justificación y Objetivos: La resistencia a los antimicrobianos se considera uno de los mayores desafíos de salud global del siglo XXI. Los antiinfecciosos son los medicamentos más utilizados en las Unidades de Cuidados Intensivos Neonatales, y su uso indebido y excesivo facilita la selección de infecciones causadas por organismos resistentes a múltiples fármacos y aumenta el riesgo de efectos adversos. El objetivo de este estudio fue evaluar la efectividad de un programa de optimización de antimicrobianos en múltiples etapas en una Unidad de Cuidados Intensivos Neonatales. **Métodos:** Estudio longitudinal cuasiexperimental con un diseño de antes y después para avaliar la implementación de intervenciones en cuatro etapas. En la etapa I, se trazó el perfil de los recién nacidos. En la Etapa II, se desarrollaron protocolos farmacoterapéuticos para medicamentos parenterales. En la Etapa III, se implementó el manejo de medicamentos parenterales en la Unidad de Tratamiento Intensivo Neonatal. En la Etapa IV, se integró una calculadora de dosis electrónica en sistema informatizado de prescripción médica. En la Etapa V, los médicos y profesionales responsables de dispensar medicamentos fueron capacitados por farmacéuticos clínicos. La efectividad se evaluó comparando la incidencia de errores de prescripción antes y después de la implementación. **Resultados:** Durante el período de implementación se realizaron 513 prescripciones: 332 de vancomicina, 149 de cefepima y 42 de piperacilina-tazobactam. Se observó una reducción estadísticamente significativa en la incidencia de errores de prescripción relacionados con la dosis y el tiempo de infusión. **Conclusiones:** La implementación de múltiples intervenciones de administración de antimicrobianos basadas en las farmacias mejoró el perfil de seguridad de las prescripciones de antimicrobianos.

Palabras Clave*: Programas de Optimización del Uso de los Antimicrobianos. Unidades de Cuidados Intensivos. Neonatales. Seguridad del paciente. Errores de medicación.*

INTRODUCTION

According to leading regulatory, economic, and political institutions, including the International Monetary Fund, the World Health Organization (WHO), the World Bank and the G8, antimicrobial resistance is one of the greatest global health challenges of the 21st century.[1]

The high incidence of infections caused by multidrug-resistant organism (MDRO) is one of the main consequences of antimicrobial resistance and a growing concern in the field of patient safety, especially in the Intensive Care Unit (ICU) and among vulnerable groups, such as neonates. Anti-infectives are the most frequently used medications in Neonatal Intensive Care Units (NICUs), and their misuse and overuse facilitate the selection of MDROs and increase the risk of adverse effects, making antimicrobial stewardship an important tool to prevent antimicrobial resistance.[2-4]

Antimicrobial stewardship is defined as "coordinated interventions designed to improve and measure the appropriate use of antimicrobial agents by promoting the selection of the optimal antimicrobial drug regimen, including dosing, duration of therapy, and route of administration".[5] In this manner, antimicrobial stewardship interventions have the potential to improve clinical outcomes and minimize harms by enhancing antimicrobial prescribing pratices.[3] Their relevance is even greater in NICUs, where very complex antimicrobial dosing regimens are used and there is still a high incidence of preventable adverse drug events involving antimicrobials.[6]

Among antimicrobial stewardship interventions, the "pharmacy-based interventions" include dose adjustment and optimization, definition of stop dates and duplicate therapy alerts, among others.[3] To streamline pharmacy-based interventions, electronic resources, such as a

Computerized Physician Order Entry (CPOE) system with clinical decision support (CDS) and standardized drug concentrations can be used and are recommended to facilitate the identification of opportunities to optimize antibiotic regimens. However, the impact of those initiatives still needs further exploration.[5]

In this context, the aim of this study was to assess the effectiveness of a multiple-step antimicrobial stewardship approach in a NICU.

METHODS

Study design and setting

This is a quasi-experimental longitudinal study in which a pre-test/post-test design was adopted to evaluate the implementation of antimicrobial stewardship interventions using retrospective data on February 2013. The study was developed according to the Standards for Reporting Implementation Studies (StaRI) statement.[7] This type of study design is encouraged by the WHO to evaluate real-world health interventions.[8]

The study took place in a 60-bed NICU of a private maternity hospital located in the city of Rio de Janeiro, Brazil. The maternity is a referral center for high-risk pregnancies and its NICU primarily cares for patients born in the hospital. The group of professionals working in the NICU was composed of a multidisciplinary team, including nurses, neonatologists, infectious diseases physicians, information technology specialists, and eleven clinical pharmacists. The clinical pharmacists had at least three years of experience. Before the intervention, medications were dispensed individually according to the prescription for each patient. The preparation and administration of medications were performed by the nursing team. Data on dispensing and administration were recorded only in the physical prescription.

Antimicrobial Stewardship interventions

The implementation of antimicrobial stewardship interventions began in August 2011 and finished in January 2013. In Stage I, which took place in August 2011, the neonates' profiles were mapped according to their sex, gestational age, birth weight and height, and antimicrobials used. The workflow involved in prescribing, dispensing, and administering parenteral drugs used in the NICU was also mapped.

Stage II took place from September to October 2011. Based on the profile identified in Stage I, the pharmacotherapeutic protocols for parenteral drugs and the standard concentration guide used in the NICU were developed. For this purpose, the following references were consulted: 2011 Neofax® textbook (Thomson Reuters, New York, USA), 2011 Lexicomp Pediatric and Neonatal Dosing Handbook (American Pharmacists Association, USA), and Handbook on Injectable Drugs (16ª Edition; American Pharmacists Association, USA).

In Stage III, from November 2011 to April 2012, intravenous admixture preparation for the NICU was implemented in the central pharmacy at the study location.

During Stage IV, conducted between October and December 2012, an electronic dosing calculator was integrated into the CPOE system. Although the entire multidisciplinary team participated in organizing the calculator, a team with information technology professionals and one pharmacist was formed during the process of implementing and integrating the calculator. It automatically calculates the appropriate concentration and dose (daily dose, unitary dose, loading dose, maintenance dose, and intervals between successive administrations) for the selected drugs using the recorded weight and age of the neonate. Additionally, the CPOE system was configured to automatically provide the appropriate reconstitution solvent, details of the dilution process (when multiple dilutions were required), and the total drug volume needed from a complete standardized drug concentration. The system also emits alerts to the prescriber whenever a medication dose is out of the recommended range.

Finally, during the three months of Stage V, the health professionals working in the NICU responsible for drug prescribing and dispensing were trained by clinical pharmacists to use and understand the electronic dosing calculator and the CPOE system with CDS. The use of the prescribing system began in January 2013.

Assessment of the effectiveness of the antimicrobial stewardship interventions

The effectiveness of the antimicrobial stewardship interventions was assessed by comparing the incidence of prescribing errors involving antimicrobials ordered to newborns before (October 2011 to December de 2012 – n=868) and after (January 2013 to March 2014 – n=915) the implementation.

To identify prescribing errors, every prescription order for cefepime, vancomycin, and piperacillin-tazobactam for the newborns in the studied NICU was evaluated. These specific antimicrobials were selected because they were the most used in the NICU according to the profile drawn in Stage I of the antimicrobial stewardship intervention.

The following prescribing errors were quantified: dose; compatibility and volume of the diluent to reconstitute the antimicrobial powder; compatibility and volume of the diluent to dilute the antimicrobial after reconstitution; final concentration of the antimicrobial after reconstitution and dilution; and time of infusion. Clinical pharmacists with at least three years of experience in clinical pharmacy in the NICU evaluated the prescription errors. The number of prescription orders for each of the aforementioned antimicrobials was also evaluated in the pre- and post-implementation periods.

Data analysis

All data were retrospectively collected from electronic medical charts available in the Enterprise Resource Planning Tasy (Philips, Netherlands). Data were statistically analyzed by the $\chi 2$-test (or Fisher's exact test when pertinent) with GraphPad Prism 8.0 to compare the pre- and post-implementation incidence of prescribing errors. Probability values of 0.05 or less were considered

significant. The characteristics (sex, birth weight and gestational age) of patients admitted before and after the implementation were compared using the t-test in order to ensure minimal influence of the patients' profile on the antimicrobial stewardship outcomes, and no statistically significant difference was identified (p<0,05).

This study is part of the project "Medications in pediatrics and neonatology: development of tools for the safe use of medicines". It was conducted in accordance with the required ethical standards – Resolutions 466/2012 - 510/2016 - 580/2018, of the Ministry of Health. The project was approved by the Brazilian Ethics Committee designated by the Ministry of Health of the Federal Government of Brazil on 18/12/2017, under CAAE registration - 82153617.5. 0000.5235, opinion number 2564476.

RESULTS

Before the implementation of the antimicrobial stewardship interventions, the NICU received a total of 884 prescription orders for antimicrobial drugs: 592 for vancomycin, 246 for cefepime, and 46 for piperacillin-tazobactam. After the implementation, although the number of newborns in the NICU increased, the total number of antimicrobial prescription orders was lower (n=513), with 332 were for vancomycin, 149 for cefepime and 42 for piperacillin-tazobactam (Figure 1).

A statistically significant reduction in the incidence of prescribing errors involving the dose, time of infusion, and diluent prescribed for all the studied antimicrobials was identified after the implementation of the antimicrobial stewardship interventions (Figure 2).

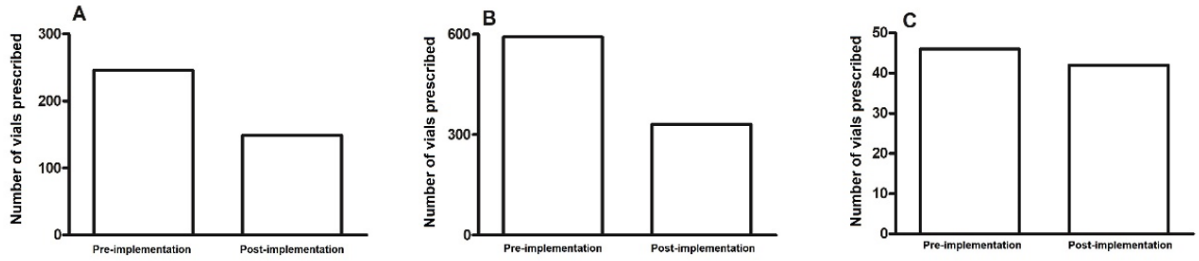

Figure 1. Number of prescription orders of cefepime (A), vancomycin (B), and piperacillin-tazobactam (C) prescribed in the period pre- and post-implementation of the antimicrobial stewardship interventions in the Neonatal and Intensive Care Unit. Rio de Janeiro, Brazil, 2013.

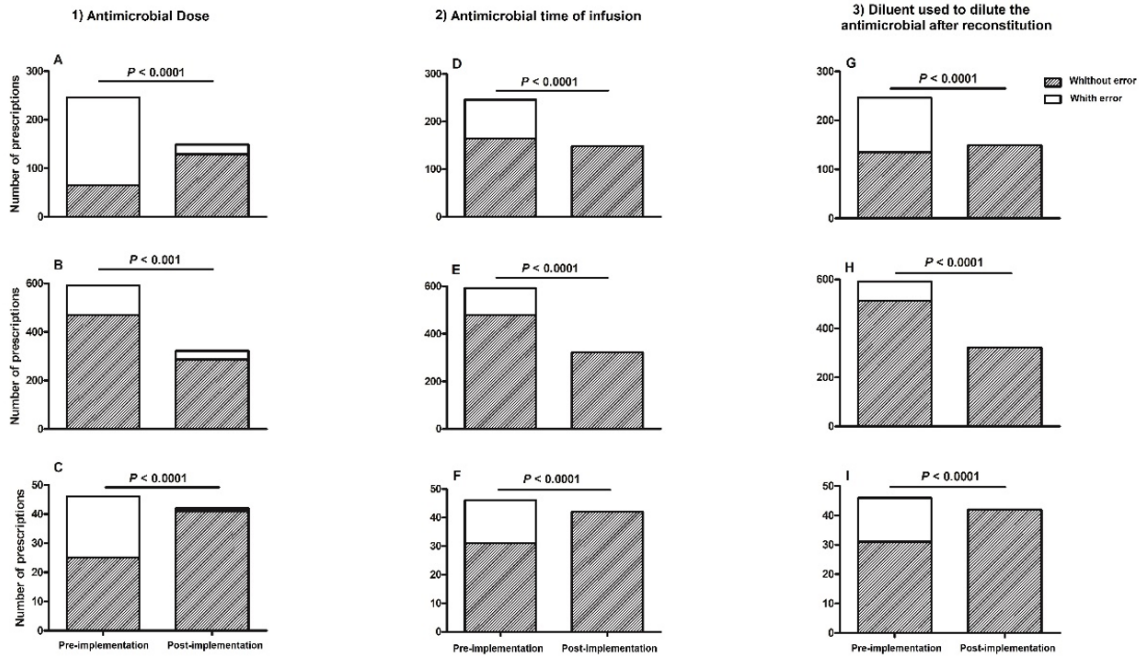

Figure 2. Comparison of the number of prescription orders with and without errors involving the (1) antimicrobial dose, (2) the antimicrobial time of infusion of cefepime, or (3) the diluent used to dilute the antimicrobial after the reconstitution for cefepime (A, D, and G), vancomycin (B, E, and H), and piperacillin-tazobactam (C, F, and I) in the period pre- and post-implementation of the antimicrobial stewardship interventions in the Neonatal and Intensive Care Unit. Rio de Janeiro, Brazil, 2013.

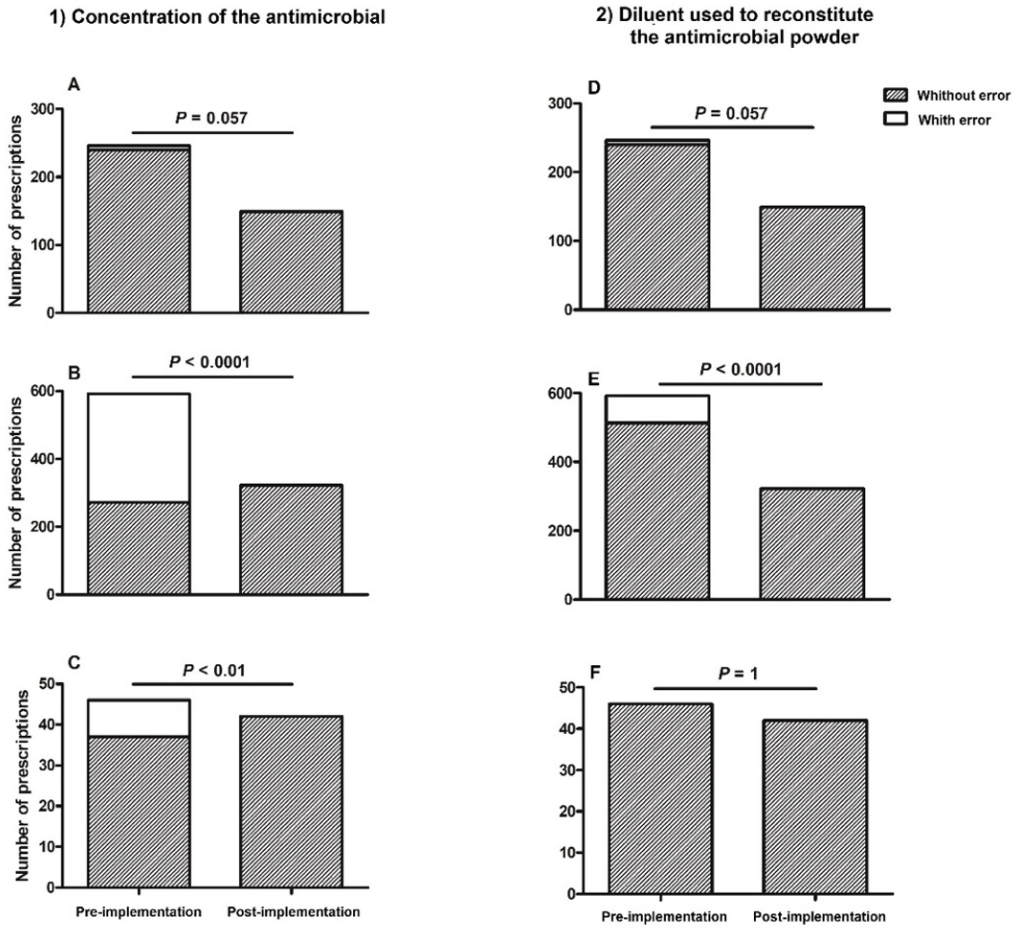

Figure 3. Comparison of the number of prescription orders with and without errors involving the (1) concentration of the antimicrobial or (2) the diluent used to reconstitute the antimicrobial powder for cefepime (A and D), vancomycin (B and E), and piperacillin-tazobactam (C and F) in the period pre- and post-implementation of the antimicrobial stewardship interventions in the Neonatal and Intensive Care Unit. Rio de Janeiro, Brazil, 2013.

Although an absolute reduction was observed in the number of prescribing errors involving the concentration of the antimicrobial after reconstitution and dilution for all the studied antimicrobials, the difference was statistically significant only for vancomycin and piperacillin-tazobactam. Additionally, a statistically significant difference in the incidence of prescribing errors involving the diluent prescribed to reconstitute the antimicrobial powder was identified only for vancomycin (Figure 3).

DISCUSSION

In the present study, the implementation of a multiple-step antimicrobial stewardship approach, which included the adoption of the CPOE system with CDS and standardized drug concentrations, had a positive impact on the incidence of prescribing errors.

Sedatives and antimicrobials are the most common class of drugs prescribed to children [9], leading to more prescription errors with antimicrobials than other agents.[9-11] Multiple pharmacy-based antimicrobial stewardship interventions were implemented in the studied NICU to avoid these errors. Note that this was made possible by involving a multidisciplinary team composed of health professionals and information technology specialists throughout the entire implementation process. Furthermore, the clinical pharmacists had prior experience and trained all the professionals involved in prescribing and dispensing drugs with the use of the CPOE system with CDS. This approach was crucial since staff inexperience and heavy workload are considered risk factors for medication errors.[12]

Overall, a reduction in prescribing errors of antimicrobial drugs was observed, especially for vancomycin. These data are extremally important because a decrease in prescribing errors for antimicrobial drugs is associated with a reduction of antimicrobial resistance, one of the greatest Global Health challenges of the 21st century.[1] Also, medication errors are the most frequent source of healthcare associated harm in the world, and according to the World Health Organization, anti-infectives should be targeted as a priority drug class when it comes to reducing avoidable harm from medicines.[13] Therefore, the implementation of effective actions to improve antimicrobial drugs utilization, such as the ones described in the present study, is paramount.

It is also important to highlight the significant

reduction in prescription orders for cefepime and vancomycin after the implementation of antimicrobial stewardship interventions, even though there was a greater number of newborns admitted to the NICU in the post-implementation period. This indicates that the pharmacy-based antimicrobial stewardship interventions might have decreased inappropriate empirical therapy with these antimicrobial drugs, one of the major important causes of antimicrobial resistance.[14] Furthermore, reducing antimicrobials prescription avoids potential side effects caused by these drugs, such as vancomycin-induced phlebitis and red man syndrome.[15,16]

In the NICU, there is a high potential for adverse drug events, and medication errors frequently involve incorrect dosages.[6, 17,18] In the present study, a decrease in prescribing errors involving inappropriate dosing was observed for all evaluated antimicrobials after the implementation of the interventions. The ideal dosage of antimicrobial is crucial for increasing the effectiveness and safety of treatment, as differences in weight and glomerular filtration rates often vary during the newborn's hospitalization.[4] A reduction in dosage prescription errors was also identified with the use of a CPOE in a study conducted in France[l], which suggested that manual prescriptions should be completely avoided in neonatal units.[19]

Errors involving the wrong diluent are also common in NICUs.[6] A significant drop in the incidence of prescribing errors involving diluents used to dilute cefepime, vancomycin, and piperacillin-tazobactam was identified. However, the errors involving diluents prescribed to reconstitute the antimicrobial powder dropped significantly only for vancomycin. Usually, sodium chloride is the diluent most frequently used by healthcare teams to reconstitute antimicrobial powders. This poses no problem for cefepime and piperacillin-tazobactam, which are compatible with this diluent. However, vancomycin powder should be reconstituted with sterile water.[20]

In the present study, a significant decrease in prescription errors involving drug concentration for vancomycin and piperacillin-tazobactam was also observed after the implementation of antimicrobial stewardship interventions. Similar results were found in a prospective cohort study developed at a children's hospital in the Netherlands, which evaluated the replacement of "free text" prescriptions with CPOE[21]. Infusion rates are frequently prescribed incorrectly to newborns in the NICU, exposing them to negative outcomes.[22] In the studied NICU, the measures adopted reduced infusion time errors for all evaluated antimicrobial drugs.

Although the findings suggest that pharmacy-based antimicrobial stewardship interventions may aid in better antimicrobial management in NICUs, it would be interesting to extend this study to less frequently used antimicrobials. Another limitation of our work was not assessing whether the implementation of the interventions could affect the clinical course of disease.

In conclusion, the implementation of multiple pharmacy-based antimicrobial stewardship interventions, including the adoption of a CPOE system with CDS and standardized drug concentrations, results in an improvement in the safety profile of antimicrobial prescriptions and contributes to safer medication practices and patient safety.

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AUTHORS' CONTRIBUTIONS

Francisco Alves Farias-Filho contributed to project management, contributed to literature search, writing of the abstract, introduction, methodology, discussion, interpretation and description of results, preparation of tables, conclusions, review and statistics. **Philipe Vieira Souza** contributed to literature search, writing of the abstract, introduction, methodology, discussion, interpretation and description of results, preparation of tables, conclusions, review and statistics. **Susana Nunes da Rocha Nascimento** contributed to literature search, writing of the abstract, introduction, methodology, discussion, interpretation and description of results, preparation of tables, conclusions, review and statistics. **Rafaela de Carvalho Rodrigues** contributed to literature search, writing of the abstract, introduction, methodology, discussion and review. **Mariana Martins Gonzaga do Nascimento** contributed to project administration, contributed to literature search, writing of the abstract, introduction, methodology, discussion, interpretation and description of results, preparation of tables, conclusions, review and statistics. **Vinicius de Frias Carvalho** contributed to literature search, writing of the abstract, introduction, methodology, discussion, interpretation and description of results, preparation of tables, conclusions, review and statistics.

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

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Hospital Santa Cruz

ORIGINAL ARTICLE

Brazilian research network on tuberculosis: scientific development Mission to eliminate tuberculosis

Rede Brasileira de Pesquisas em Tuberculose (REDE-TB): missão de desenvolvimento científico para eliminar a tuberculose

Red brasileña de investigación en tuberculosis: misión de desarrollo científico para eliminar la tuberculosis

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Corresponding Author:
Rander Junior Rosa
rander1junior@gmail.com

Av. dos Bandeirantes, 3900 - Campus Universitário - Bairro Monte Alegre, Ribeirão Preto, São Paulo, Brasil.

Rander Junior Rosa[1];
Ana Beatriz Marques Valença[1];
Letícia Perticarrara Ferezin[1];
Natacha Martins Ribeiro[1];
Paula Daniella de Abreu[1];
Rubia Laine de Paula Andrade[1];
Willie Otávio Bueno Bernardi[1];
Diogo Henrique Mendes da Silva[1];
Aline Aparecida Monroe[1];
Erica Chimara Silva[2];
Vânia Maria Silva Araújo[1];
Anna Cristina Calçada Carvalho[3];
Ethel Leonor Noia Maciel[4];
Ana Paula Junqueira-Kipnis[5];
Jose Roberto Lapa e Silva[6];
Lia Gonçalves Possuelo[7];
Ricardo Alexandre Arcêncio[1];

[1] *Universidade de São Paulo, Ribeirão Preto, SP, Brazil.*
[2] *Instituto Adolfo Lutz, São Paulo, SP, Brazil.*
[3] *Instituto Oswaldo Cruz, Rio de Janeiro, RJ, Brazil.*
[4] *Universidade Federal do Espírito Santo, Vitória, ES, Brazil.*
[5] *Universidade Federal de Goiás, Goiânia, Goiás Brazil.*
[6] *Universidade Federal Fluminense, Niterói, RJ, Brazil.*
[7] *Universidade de Santa Cruz do Sul, Santa Cruz, RS, Brazil.*

ABSTRACT

Background and Objectives: Since its inception, the Brazilian Tuberculosis Research Network (REDE-TB) has contributed significantly to scientific and technological advances in Brazil. This study analyzes this contribution in the strategic areas of tuberculosis prevention, diagnosis, and treatment, which are relevant for achieving the 2030 Agenda to End Tuberculosis**. Methods:** This research is based on a survey of the Lilacs and Embase/MEDLINE databases, focusing on primary and secondary studies on tuberculosis published by members of REDE-TB between 2018 and 2023. Data on identification, scope, study location, design, area, and population studied were extracted. Descriptive statistics and georeferencing were used for the analysis**. Results:** A total of 670 publications were identified, of which 447 were included in the review. Of these, 315 (70.5%) were published in international journals. Most studies in Brazil were conducted in Rio de Janeiro (29.0%), followed by São Paulo (19.2%), Rio Grande do Sul (13.8%), Paraná (11.6%) and Amazonas (10.7%). After Brazil, 24 (8.0%) studies were conducted in India, followed by South Africa (16 - 5.3%)

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and Uganda (10 - 3.3%). The studies had different designs, including literature reviews and epidemiologic studies, and focused primarily on tuberculosis disease (56.4%) and, to a lesser extent, tuberculosis infection (12.6%). **Conclusions:** The study highlights the importance of the Brazilian Research Network on Tuberculosis (REDE-TB) in the scientific production related to tuberculosis, contributing to policies and actions aimed at combating the disease in Brazil and around the world**.**

Keywords: *Tuberculosis. Latent Tuberculosis. Technology.*

RESUMO

Justificativa e Objetivos: Desde seu lançamento, a Rede Brasileira de Pesquisas em Tuberculose (REDE-TB) tem contribuído significativamente para a produção científico-tecnológica no Brasil. Este estudo teve como objetivo buscar essa contribuição nas áreas estratégicas de prevenção, diagnóstico e tratamento da tuberculose, relevantes para o cumprimento da Agenda 2030 para o Fim da Tuberculose. **Métodos:** A pesquisa foi baseada em um levantamento nas bases de dados *Lilacs* e *Embase/MEDLINE*, focando em estudos primários e secundários sobre tuberculose publicados entre 2018 e 2023 vinculados à REDE-TB. Foram extraídos dados de identificação, abrangência, local de estudo, delineamento, área e população estudada. A análise utilizou estatística descritiva e georreferenciamento. **Resultados:** Identificou-se 670 publicações, com 447 incluídas na revisão. Dentre estas, 315 (70,5%) foram publicadas em periódicos internacionais. A maioria dos estudos no Brasil ocorreu no Rio de Janeiro (29,0%), seguido por São Paulo (19,2%), Rio Grande do Sul (13,8%), Paraná (11,6%) e Amazonas (10,7%). Após o Brasil, 24 (8,0%) estudos foram realizados na Índia, seguidos pela África do Sul (16 - 5,3%) e Uganda (10 - 3,3%). Os estudos apresentaram delineamentos variados, incluindo revisões de literatura e estudos epidemiológicos, com foco principal em tuberculose doença (56,4%) e, em menor proporção, em tuberculose infecção (12,6%). **Conclusão:** O estudo evidencia a importância da Rede Brasileira de Pesquisas em Tuberculose (REDE-TB) na produção científica e tecnológica sobre TB, contribuindo no desenvolvimento de estratégias de enfrentamento à doença no Brasil e no mundo.

Descritores: *Tuberculose. Tuberculose Latente. Tecnologia.*

RESUMEN

Justificación y Objetivos: Desde su lanzamiento, la Red Brasileña de Investigaciones en Tuberculosis (REDE-TB) ha contribuido significativamente a la producción científico-tecnológica en Brasil. Este estudio tuvo como objetivo analizar dicha contribución en áreas estratégicas de prevención, diagnóstico y tratamiento de la tuberculosis, relevantes para el cumplimiento de la Agenda 2030 para el Fin de la Tuberculosis. **Métodos:** Esta investigación se basó en un levantamiento en las bases de datos *Lilacs* y *Embase/MEDLINE*, centrándose en estudios primarios y secundarios sobre tuberculosis publicados entre 2018 y 2023 por miembros de la REDE-TB. Se extrajeron datos de identificación, alcance, lugar de estudio, diseño, área y población estudiada. El análisis utilizó estadística descriptiva y georreferenciación. **Resultados:** Se identificaron 670 publicaciones, de las cuales 447 fueron incluidas en la revisión. Entre estas, 315 (70,5%) fueron publicadas en revistas internacionales. La mayoría de los estudios en Brasil se realizaron en Río de Janeiro (29,0%), seguido de São Paulo (19,2%), Río Grande do Sul (13,8%), Paraná (11,6%) y Amazonas (10,7%). Después de Brasil, 24 (8,0%) estudios se realizaron en India, seguidos por Sudáfrica (16 - 5,3%) y Uganda (10 - 3,3%). Los estudios presentaron diseños variados, incluyendo revisiones de literatura y estudios epidemiológicos, con un enfoque principal en la enfermedad por tuberculosis (56,4%) y, en menor proporción, en la infección por tuberculosis (12,6%). **Conclusión:** El estudio evidencia la importancia de la Red Brasileña de Investigaciones en Tuberculosis (REDE-TB) en la producción científica sobre tuberculosis, contribuyendo a políticas y acciones para enfrentar la enfermedad en Brasil y en el mundo.

Palabras Clave*:* *Tuberculosis. Tuberculosis Latente. Tecnología.*

INTRODUCTION

Tuberculosis (TB) is the deadliest infectious disease in the world, mainly affecting people living in poor and/or developing countries. Brazil is among those countries that face many challenges in eliminating TB, with 11 states having a TB incidence rate higher than the national average in 2023 (37.0/100,000 inhabitants) and a mortality rate of 2.2/100,000 inhabitants.[1, 2]

National efforts are being made to end TB as an epidemic by 2030, and eliminate the disease by 2050 (< 10 cases per 100,000 inhabitants). The End TB Strategy, launched in 2015, is based on three fundamental pillars for achieving the goals: user-centered care, bold social policies that impact the life course of people with TB and their families, and intensified research and innovation.[3]

Research and innovation are essential aspects for achieving the goal of eliminating TB and, today, the current priorities on a global scientific agenda include a TB vaccine with greater efficacy than the current one (BCG); shorter treatments for sensitive TB (up to 4 months of treatment) and resistant TB (up to 6 months and 100% by mouth), point-of-care diagnostics, and monitoring and surveillance of resistant TB, with molecular biology tech-

nologies; and person-centered care and social support, with a reduction in catastrophic costs.[3]

Among the care paradigms, the proposal is to move away from the curative, disease-centered model towards prevention, with a focus on TB preventive treatment (TPT) for priority groups and the elimination of barriers to access to TB diagnosis and treatment, especially among vulnerable populations. In addition, the use of new digital technologies and Artificial Intelligence (AI) could be of great help in the active search for cases, in increasing diagnostic accuracy and in carrying out educational activities on TB.[4]

Among the various initiatives to leverage science and technology in the field of TB, research cooperation networks stand out. Through the integration of strategic areas, interfacing basic and applied sciences, speed is promoted in the production of inputs and strategic and technological incorporation into the Unified Health System (SUS), thus bringing sustainable and creative solutions to health services.[5]

On the national scene, we would highlight the Brazilian Tuberculosis Research Network (REDE-TB), which was launched to compete for CNPq's Millennium Institutes Call for Proposals in 2002. Its epistemological matrix was systemic thinking, cooperation and solidarity among peers, and its operational strategy was to identify potential leaders to contribute to shaping a National TB Research Agenda. Civil society and government representatives were included in REDE-TB's organizational structure. Since its launch, there have been important developments at the national level, when TB began to occupy the health agenda, and REDE-TB members took over the National Technical Advisory Committee (CTA) of the Ministry of Health's now-defunct National TB Program (PNCT). [6-8]

At the international level, the World Health Organization (WHO) invited REDE-TB to take part in the Task Force for Movement Research in 2009, as it is a very innovative and peculiar way of producing science and technology. There is evidence that REDE-TB can act as one of the major locomotives and promoters of science and technology around TB in Latin America, making it important to verify this hypothesis through a literature review. With this in mind, this review sought to analyze REDE-TB's contribution to the technical-scientific development of TB over the last five years, with the aim of demarcating its contributions to the advancement of the End TB strategy.[9]

METHODS

Study design

A bibliographic review was carried out to construct the state of the art with the aim of exploring a wide and diverse range of studies that have been published by REDE-TB researchers, as well as their capacity to include both empirical and theoretical literature.[10]

This type of review aims to provide fundamental information on the institutional and social basis of the research field, the strategies for communicating and disseminating knowledge and the thematic, theoretical, methodological and epistemological trends. Its importance lies in describing, mapping, monitoring and evaluating the development and consolidation of the field.

The study was carried out in three stages: identification of REDE-TB members and their publications; data extraction; and synthesis of the literature results,

REDE-TB, created in 2002, currently covers eighteen areas of research related to TB, divided into thematic axes: drug development; health technologies and innovation; human resources; tuberculosis and HIV; clinical trials; tuberculosis in indigenous people; pediatric tuberculosis; tuberculosis in prisons; operational research; multidrug-resistant tuberculosis; epidemiology: information and informatics; quality management, knowledge and information management; biosafety and infection control; social mobilization; non-tuberculous microbacteria; international relations; interaction with government and social protection. These axes are made up of specialized researchers, distributed according to their expertise and contribution.

Identification of REDE-TB members and their publications

The process of identifying REDE-TB members took place by consulting the minutes of its extraordinary and ordinary assemblies held between 2018 and 2023. REDE-TB assemblies involve the participation of area coordinators and vice-coordinators, as well as associate members.

For access to these minutes, authorization was requested from the REDE-TB board. All the names of the people taking part in the meetings were taken into account when searching for publications in the LILACS and Embase/MEDLINE databases, together with the descriptors 'Tuberculosis', 'Tuberculosis' and 'TB'.

The searches were conducted in September 2023 and there were no restrictions on the language of publication. However, it was restricted to studies published after 2018, since that year saw the launch of the Global Plan to End TB (2018-2022) and the United Nations High-Level Meeting on TB, which was an important milestone in defining policies for TB research priorities and funding for United Nations Member States.[10]

Screening and selection of publications

The data obtained from the databases was exported and compiled on the Rayyan platform, which made it possible to detect and eliminate duplicate publications.[11,12]

Once the duplicate publications had been eliminated, the full articles were searched for, seeking to include in the review those that directly addressed TB and that had been published in the last five years by researchers linked to REDE-TB, regardless of the order of authorship. Excluded from the study were letters, editorials, commentaries, study protocols, conference abstracts, case reports, studies related to Mycobacterium Non-Tuberculosis or whose main focus was another infection/disease (HIV, dengue, COVID-19) without focusing on TB, as well as articles whose authors were not part of REDE-TB.

Data extraction

At this stage, data was extracted from the studies included in the review. The variables of interest were previously defined and included the following items: authors; title; year of publication; journal; language of publication; funding agency; scope of the study; state where the study was carried out; country where the study was carried out; study design; study area; study population. Articles published in various journals were collected, identifying their impact factor. Data extraction was carried out by five researchers and then checked in its entirety by a reviewer.

Summary of results

The data extracted was analyzed using descriptive statistics (absolute and relative frequency distribution). Subsequently, for the georeferencing stage of the studies published in Brazil and worldwide according to study site, we used the meshes in .shp format made freely available by the IBGE (states of Brazil) and the Environmental Systems Research Institute (world map). These sites were exported to QGIS software v. 3.32.3, georeferenced according to the geographical coordinates in their respective territorial meshes and thematic maps of the Brazilian states and countries were then generated.

Ethical aspects

In this study, due to the nature of the research, approval by the Research Ethics Committee (REC) was not required. The legislation that waives the need for approval by the REC generally applies to studies that do not directly involve human beings, such as literature reviews. Article 1 of Resolution 510/2016 mentions that research which does not directly involve human beings or which uses information in the public domain or anonymized data can be exempt from ethical evaluation.

RESULTS

By consulting the minutes of the REDE-TB meetings, 77 members were identified, with at least one researcher in each research area.

After identifying the researchers linked to REDE-TB, a review was carried out. A total of 670 publications were identified, of which 117 were excluded for being duplicates and another 106 for not having REDE-TB members as authors, 447 publications were included in this review (Figure 1).

Among the studies included in this review, the data on the impact factor of the publications analyzed stands out: 59 (12.53%) articles were published in journals with no impact factor; 279 (62.39%) in journals with an impact factor between 0.2 and 3; 73 (16.34) in journals with an impact factor between 4 and 10; 26 (5.16%) in journals with an impact factor between 11 and 20; and 13 (3.58%) in journals with an impact factor greater than 21. In addition, 78 (17.4%) were published in 2018; 78 (17.4%) in 2019; 96 (21.5%) in 2020; 90 (20.1%) in 2021; 80 (17.9%) in 2022; and 25 (5.6%) in 2023, up to the time of data analysis. As for the journals of publication, 315 (70.5%)

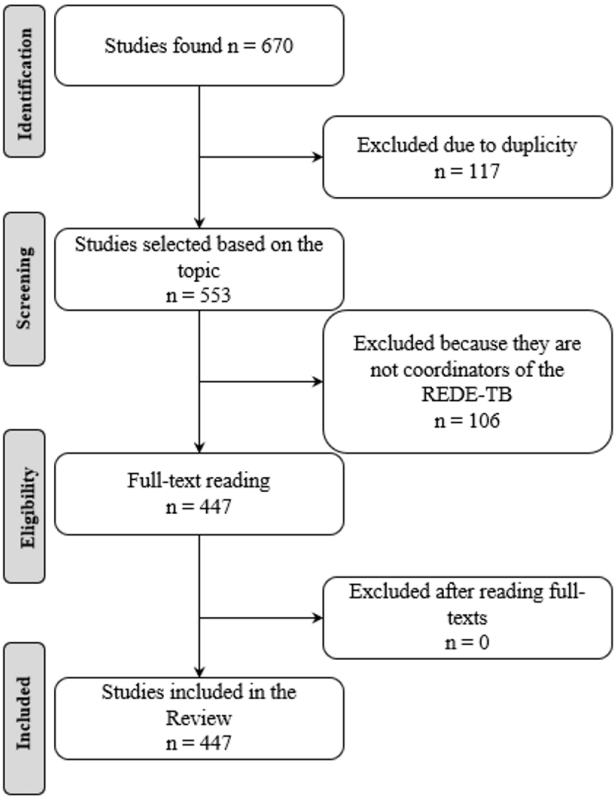

Figure 1. Flowchart illustrating the process of identification, screening and inclusion/exclusion of studies, 2018 to 2023.

were international, 426 (95.3%) were published in English.

Of the 447 studies included, 72 (16.1%) did not mention any funding agency and 20 (4.5%) reported that there was no funding. Of the 355 studies that received funding, 195 (54.9%) were funded by CNPq, 158 (44.5%) by international agencies, 154 (43.4%) by state foundations, 148 (41.7%) by CAPES, 49 (13.8%) by the Oswaldo Cruz Foundation, 33 (9.3%) by the federal government and 63 (17.7%) by various other bodies. Some studies received support from more than one funding agency.

Of the studies carried out, 224 (50.11%) were conducted in some Brazilian state. Rio de Janeiro was the state where most of the studies were carried out (65 - 29.0%), followed by São Paulo (43 - 19.2%), Rio Grande do Sul (31 - 13.8%), Paraná (26 - 11.6%) and Amazonas (24 - 10.7%), (Figure 2). It is important to note that some of the studies analyzed were carried out in more than one location within the states. For this reason, the number of 308 shown on the map (Figure 2) refers to the specific locations within the states where these studies were carried out. With this, it was possible to verify the scope of studies at a national level.

It was possible to identify the country in 301 (67.25%) studies. After Brazil, with 224 (89.0%) studies developed, India was the country with the largest number of studies, totaling 24 (8.0%) studies developed in partnership with REDE-TB researchers, followed by South Africa with 16 (5.3%) and Uganda with 10 (3.3%) (Figure 3). It is im-

portant to note that the total of 463 shown on the map (Figure 3) refers to the locations of the studies carried out, and not the total number of studies, since some of them were conducted in more than one country. It is therefore possible to see the scope of the studies worldwide.

As for the design of the studies conducted by REDE-TB researchers, 56 (12.5%) were literature reviews; 56 (12.5%) were cross-sectional studies; 55 (12.3%) were in vitro studies; 49 (11.0%) were prospective cohorts; and 43 (9.6%) were ecological studies (Table 1).

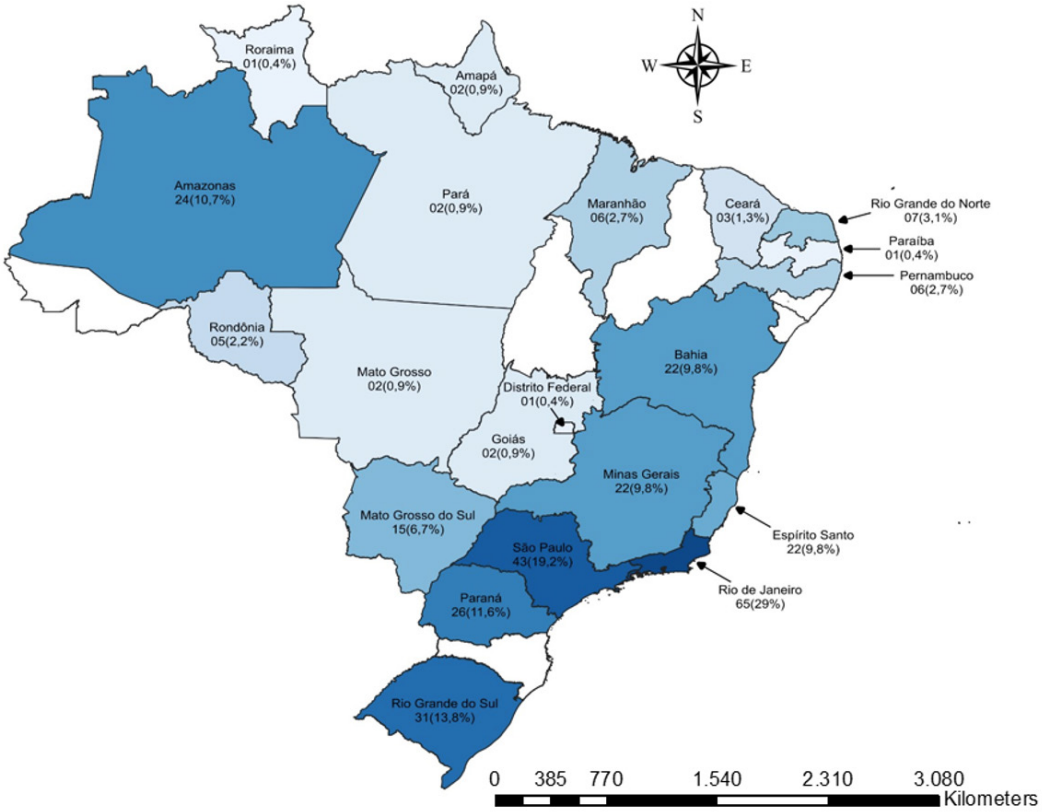

Figure 2. Distribution of studies conducted by REDE-TB researchers, by federation unit, Brazil, 2018 to 2023.

*Caption: *More than one unit of the federation was addressed in some studies, so the cumulative percentage exceeds 100%; in addition, 223 studies were not considered in this analysis because they did not cite this variable or because this variable did not apply to the study in question. The high frequency of studies per state is represented by dark shades, while light shades indicate a lower number of studies in that state."*

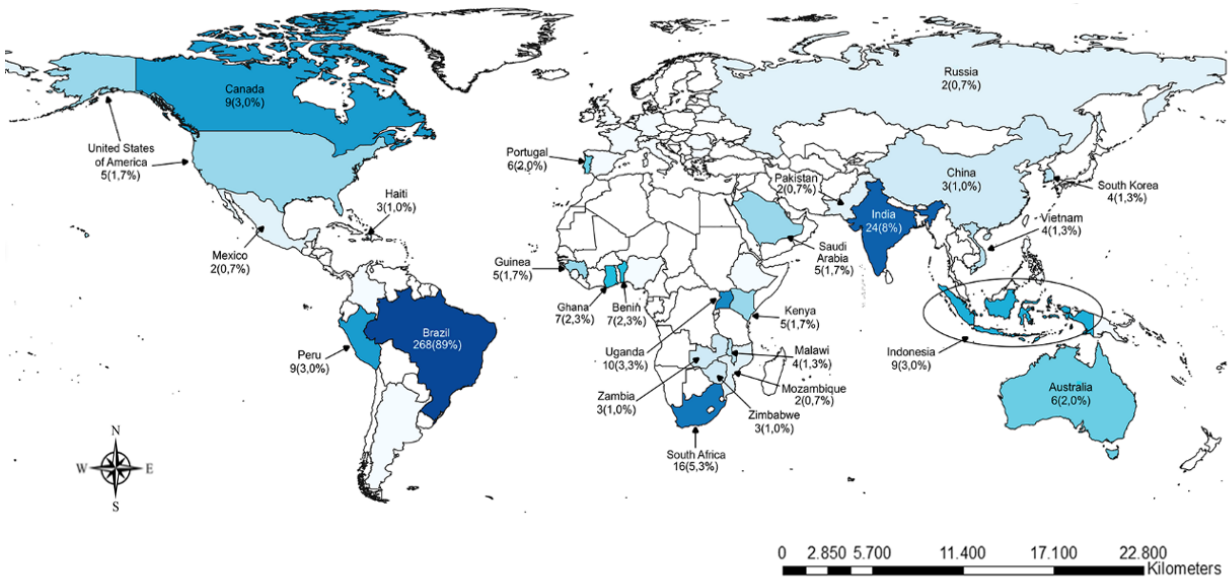

Figure 3. Distribution of studies conducted by REDE-TB researchers, by country of study, Brazil, 2018 to 2023*

*Caption: *Countries with one study each have not been marked on the map. They are: Argentina, Belarus, Bulgaria, Colombia, Ethiopia, France, Gambia, Georgia, Guinea-Bissau, Germany, Italy, Nigeria, Papua New Guinea, Romania, Sierra Leone, Singapore, Spain. More than one country was covered in some studies, which is why the cumulative percentage exceeds 100%; 146 studies were not considered in this analysis because they did not mention this variable or because this variable did not apply to the study in question.*

Table 1. Distribution of studies conducted by REDE-TB researchers, by design, Brazil, 2018 to 2023.

Category	Study Design	N (%)*
PRIMARY		
Observational	Cross-sectional	56 (12.5)
Quantitative	Prospective cohort	49 (11.0)
	Ecological	43 (9.6)
	Retrospective cohort	38 (8.5)
	Case-control	21 (4.7)
	Descriptive	26 (5.8)
Qualitative	Qualitative	9 (2.0)
Mixed	Mixed methods	1 (0.2)
Measurement/Evaluation	Accuracy of diagnostic tests	19 (4.3)
	Cost/cost-effectiveness	15 (3.4)
	Others	27 (6.1)
EXPERIMENTAL		
	in vitro	55 (12.3)
	Intervention study	3 (0.7)
	in vivo	30 (3.7)
	in silico	3 (0.7)
	Clinical trial	15 (3.4)
SECUNDARY	Literature Review	56 (12.5)

*Caption: *Some studies had more than one design, so the cumulative percentage exceeds 100%.*

As for the area of approach of the studies, 145 (32.4%) were focused on epidemiology, of which 32 were spatio-temporal studies. Other areas of study that were widely covered were: development and/or evaluation of drugs/treatment regimens (20.4%); clinical studies (16.1%) on pathogenesis, immunology and genetic markers; and development and/or evaluation of diagnostic methods (10.1%). Other areas of study can be identified in Table 2.

Table 2. Distribution of studies conducted by REDE-TB researchers, by area of study, Brazil, 2018 to 2023.

Areas of study	N (%)*
Epidemiology	145 (32.4)
Development and/or evaluation of drugs/treatment regimens	91 (20.4)
Clinical studies (pathogenesis/immunology/prognosis/ genetic markers)	72 (16.1)
Development and/or evaluation of diagnostic methods	45 (10.1)
Operational studies	39 (8.7)
Genetics and distribution of MTB	23 (5.1)
Evaluation and interoperability of information systems/ research data or artificial intelligence or digital health	18 (4.0)
Social perceptions and representations	6 (1.3)
Economic evaluation (catastrophic expenditure study)	6 (1.3)
Development and/or evaluation of medicinal plants	6 (1.3)
Knowledge, attitudes and practices in tuberculosis	4 (0.9)
Creation and/or development of vaccines	2 (0.4)
Validation of data collection instruments	2 (0.4)
Health care/ Access	1 (0.2)
Social network/social protection	1 (0.2)
Quality of life for people affected by TB	1 (0.2)

Caption: MTB: Mycobacterium tuberculosis; TB: tuberculosis
**Some studies covered more than one area, so the cumulative percentage exceeds 100%.*

The studies covered a variety of populations, with the most frequent being people with TB "disease" (56.4%). People with TB infection were addressed in 55 (12.6%) studies and co-infection with HIV was the subject of 38 (8.7%) studies. Other populations addressed by the studies can be identified in (Table 3).

Table 3. Distribution of studies conducted by REDE-TB researchers, according to study population, Brazil, 2018 to 2023.

Study population	N (%)*
TB disease	246 (56,4)
TB infection	55 (12,6)
TB/HIV co-infection	38 (8,7)
Children and adolescents	28 (6,4)
Healthcare or prison staff/managers/students	25 (5,7)
MTB strains/clinical isolates	25 (5,7)
Contacts	24 (5,5)
People deprived of their liberty	21 (4,8)
Respiratory symptomatic patients	19 (4,4)
People with diabetes mellitus/dysglycemia	18 (4,1)
Operational Studies of Treatment Outcomes	17 (3,9)
Animals (zoonotic TB)	14 (3,2)
Indigenous people	7 (1,6)
Homeless population	6 (1,4)
Operational studies of health services	6 (1,4)
International Migrants, Refugees and Stateless Persons	6 (1,4)
People who use psychoactive substances	5 (1,1)
People living with HIV	5 (1,1)
COVID-19	4 (0,9)
Suspected extrapulmonary TB	4 (0,9)
People with post-TB	4 (0,9)
Mental disorders	3 (0,7)
Transgender people	2 (0,5)
Pregnant women	2 (0,5)
People vaccinated with BCG	1 (0,2)
Renal insufficiency	1 (0,2)
Rheumatological diseases	1 (0,2)
Riverside population	1(0,2)

*Caption: *Some studies had more than one type of population, so the cumulative percentage exceeds 100%.*

DISCUSSION

With this investigation, we sought to analyze REDE-TB's contribution to the technical-scientific development of TB over the last five years, describing its contributions to the advancement of the strategy to end TB. A significant amount of scientific production can be observed, covering the 18 areas of knowledge that currently make up the network.

The results show a significant concentration of studies in some states and regions of Brazil, such as Rio de Janeiro and São Paulo, while others have no studies affiliated to REDE-TB. This suggests the need for strategies to expand the Network's activities, such as encouraging the inclusion of new researchers from these regions or

promoting collaborative studies involving local professionals and civil society. These initiatives could increase the representativeness and equity in the distribution of TB research efforts in the country (https://doi.org/10.6084/m9.figshare.27170853.v1).

Among the scientific-technological productions, we can see REDE-TB's contribution to the development of new treatment regimens, shortened treatments, vaccines, diagnostic tests, as well as studies evaluating diagnostic accuracy, cost-effectiveness and economic evaluations, especially with regard to catastrophic costs, which impact on the quality of life of patients and families. Artificial intelligence was also a technology evaluated by our researcher.[13-16]

We also noticed that the studies go beyond the national scenario, taking place in partnership with India and South Africa to a greater extent. This finding may have been due to the launch of the BRICS-TB NETWORK in 2017, the aim of which was technical-scientific cooperation between the countries that make up this bloc. In order to promote scientific collaboration in TB between the BRICS countries. In 2019, there was a specific call for proposals from the Department of Science and Technology (DECIT), together with the National Council for Scientific and Technological Development (CNPq), which included the participation of several REDE-TB members (Call MS-SCTIE-Decit / CNPq No. 33/2019 - Research on Tuberculosis within the BRICS).[17]

Another important finding is that the studies interface with many countries, which shows the capillarity of REDE-TB and its interconnections. In Latin America, on the other hand, there is still a gap to be filled, as has already been shown by studies on TB that point to low cooperation between Brazil and Latin American countries. A meeting was held in Chile in mid-August 2024, with representatives of civil society from Argentina and/or Mexico, Peru, Colombia, Uruguay, Paraguay, El Salvador, the United States, Guatemala, Panama, Brazil and Chile, where the creation of a Latin American TB-NET was envisioned, with the expectation of more cooperation between the countries and, therefore, to advance the Elimination of TB on the continent.[18]

When we look at the temporal distribution of scientific publications on TB produced by REDE-TB, we notice a relatively uniform distribution over the years, with a slight increase in the years 2020 and 2021, these being the most critical years of the COVID-19 pandemic. This increase can be attributed to the growing awareness of the interconnection between infectious diseases, the urgency of generating evidence to inform health policies and the impact of COVID-19 on tuberculosis prevention and control. Studies show that the pandemic has highlighted the need to investigate how COVID-19 affects the management of diseases such as tuberculosis, influencing both access to treatment and transmission. In addition, researchers have adapted their approaches to deal with these new realities, demonstrating resilience and an ongoing commitment to public health.[19-21]

It can also be seen that the majority of articles were published in international journals, with a selective editorial policy and arbitration, and this is probably due to the weight and penetration of REDE-TB, including its recognition by the WHO and Stop-TB. We also found that the results reveal a solid relationship between publications and research funding agencies.

As for the sources of funding, the diversity pursued by the researchers is remarkable, encompassing international agencies such as the Stop TB Partnership, the National Institute of Health (NIH), the United States, among others, and state foundations and government bodies such as CNPq and CAPES. A relevant finding is that 20.6% of the studies listed did not mention a funding agency, which can be attributed to the fact that the studies did not have their own funding, indicating that the research was conducted voluntarily and/or with resources from the researchers' own institutions. We would like to highlight the difficulties faced by researchers in obtaining funding, especially in the area of TB, which since 2019 has had a blackout, with no thematic funding, which has probably contributed to maintaining the situation.[22]

From the content analysis of the studies, it can be seen that many operational studies took place in hospital environments, outpatient units and basic health units. A significant proportion of the studies had a municipal scope, reflecting the interest of REDE-TB researchers in public health issues at a local level. We also observed a small proportion of studies in indigenous territories and universities, showing a diversity of interests in the fields of TB study, with approaches in different geographical and cultural contexts.[23,24]

With regard to the national scope of the studies, states such as Rio de Janeiro and São Paulo, which have large research and development centers, contributed almost half of the projects carried out with the participation of REDE-TB. However, Rio Grande do Sul, Paraná and Amazonas also contributed, together accounting for 36.1% of the studies. The fact that the studies were carried out in different states can be attributed to various factors, including the availability of resources, the focus of the research and the presence of universities and research institutes focused on the study of TB.[25-27]

It is also worth highlighting the plurality of types of research being carried out by REDE-TB members, with a predominance of literature reviews, experimental studies (involving pre-clinical studies, vaccines and treatment regimens and clinical trials, with a majority of diagnostic tests) and quasi-experimental, epidemiological studies (being descriptive, cross-sectional, cohort, case-control and ecological, the latter consisting of geospatial studies and including time series analysis). It is important to note that genetic studies are being carried out to map and monitor resistance, such as whole genome sequencing (WGS), mutation analysis associated with resistance and phenotypic virulence tests.

As far as the approach of the studies is concerned, there was a predominance of epidemiological studies. Analyzing the distribution of TB, especially in the Brazilian scenario, contributes to discussions about the health-disea-

se process and the determining factors for the involvement and outcomes of the disease in the different regions of the country, as well as contributing to the implementation of social and health policies for universal access to early diagnosis and treatment, control of transmissibility and an increase in favorable outcomes.[27-29]

In addition, studies aimed at the development and/or evaluation of drugs/treatments, as well as clinical studies and the development/evaluation of diagnostic methods made up an important sample of this review. This scientific evidence, together with epidemiological studies, can have an impact on improving health actions with a view to early diagnosis and treatment, as well as the quality of life of people affected by TB.[30]

With regard to the distribution of the studies conducted by REDE-TB researchers, there was a significant diversity in the populations studied in relation to TB and its various forms, including disease and infection. Most of the studies focused on people with pulmonary TB, the most prevalent clinical form and of greatest epidemiological importance, due to the potential for transmission. The literature shows that pulmonary TB is also one of the leading causes of death worldwide, accounting for the largest number of deaths caused by a single infectious agent, making its elimination a priority compared to other infectious diseases due to its impact on global health.[31]

It is also notable that a significant percentage of studies deal with people with TB infection, since it is important to understand and discuss not only manifest cases of the disease, but also those in which the infection is present without obvious clinical symptoms. It is estimated that approximately 25% of the world's population is infected with MTB (Mycobacterium tuberculosis), and the disease develops in 5-10% of these cases over the course of their lives, with a higher risk in immunocompromised groups. Therefore, latent TB can represent a significant challenge for TB control programs, since these people may develop active disease in the future.[32]

Although the number of studies on TB with HIV/AIDS co-infection has been substantially low compared to the others, this does not diminish its importance due to its impact on the prognosis of cases, as well as the challenges encountered in concomitant treatment and control of the infection/disease. This is because, in 2016, 57% of people reported with TB were infected with HIV and also because, in Brazil, there are signs of a re-emergence of the AIDS epidemic, with the worst indicators in 30 years, including an increase in cases among homosexuals and concentration in urban centers. Thus, TB/HIV co-infection requires an integrated and coordinated approach between control programs, highlighting strategies such as early diagnosis and timely treatment.[33,34]

Mathematical models have come up with estimates that analyze strategies and trends for achieving the targets set, allowing managers and authorities around the world to check whether their countries will succeed in achieving them[3]. According to these models, if we continue as we are, with no progress in terms of social protection policies and no incentives for research and innovation in TB, the expectation is that we will reach the target beyond 2050. However, if combined with the two pillars mentioned above, we can expect to achieve it in good time.[35-37]

Finally, it should be noted that the studies were part of diverse areas of study and addressed different population groups not covered in this discussion, but which can be identified in the results, showing the diversity and potential for action by REDE-TB researchers on the subject of TB.

It is worth noting that between 2012 and 2021, there was a significant increase in new cases of pulmonary tuberculosis (TB) among self-declared black or brown people, from 61.9% to 69.0%, while cases among whites fell from 35.9% to 28.9%. The percentage of cases among yellow or indigenous people remained constant at around 2.1%. This shows that it is essential to expand the active search and strengthen collaboration between the health services of the Unified Health System (SUS) and other institutions, taking into account the specificities of the most vulnerable populations, such as people deprived of their liberty, homeless people, immigrants and indigenous people.[38]

As for the limitations of this study, it is worth noting that studies carried out by REDE-TB researchers who were absent from the assemblies were not included. It is also important to recognize as a limitation the fact that the search was carried out in only three databases and with a time frame which, for the most part, included the period of the COVID-19 pandemic, which may have resulted in an atypical production of studies involving TB. Despite these limitations, this review has the potential to show a picture of what REDE-TB has been contributing to scientific research on TB in Brazil and around the world.

The study shows the importance of REDE-TB's work in scientific production on TB around the world, which is recognized by national and international funding agencies and materialized in the production of studies with different methodological designs and in different study sites, areas of knowledge and population groups. It is also worth highlighting the internationalization of the knowledge produced by its members, in response to the requirements for obtaining research grants and the classification of Graduate Programs, as well as in policies and actions to combat TB

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AUTHORS' CONTRIBUTIONS

Rander Junior Rosa contributed to the bibliographical research, writing the abstract, introduction, methodology, discussion, interpretation and description of the results, drawing up tables, conclusions, review and statistics**. Ana Beatriz Marques Valença** contributed to the bibliographical research, writing the abstract, introduction, methodology, discussion, interpretation and description of the results, drawing up tables, conclusions, review and statistics**. Letícia Perticarrara Ferezin** contributed to project management, bibliographical research, writing the abstract, introduction, methodology, discussion, interpretation and description of results, conclusions, review**. Natacha Martins Ribeiro** contributed to project management, bibliographical research, writing the abstract, introduction, methodology, discussion, interpretation and description of results, conclusions, review**. Paula Daniella de Abreu** contributed to the writing of the abstract, methodology, interpretation of results, conclusions, review**. Rubia Laine de Paula Andrade** contributed to project management, bibliographical research, writing the abstract, introduction, methodology, discussion, interpretation and description of results, conclusions, review and statistics**. Willie Otávio Bueno Bernardi** contributed to project management, bibliographical research, writing the abstract, introduction, methodology, discussion, interpretation and description of results, conclusions, review**. Diogo Henrique Mendes da Silva** contributed to the writing of the abstract, methodology, interpretation of results, conclusions, review**. Aline Aparecida Monroe** contributed to project management, bibliographical research, writing the abstract, introduction, methodology, discussion, interpretation and description of results, conclusions, review**. Erica Chimara Silva** contributed to the writing of the abstract, methodology, interpretation of results, conclusions, review**. Vânia Maria Silva Araújo** contributed to project administration, fund acquisition, bibliographic research, review and statistics**. Anna Cristina Calçada Carvalho** contributed to writing the abstract, revision. **Ethel Leonor Noia Maciel** contributed to project management, bibliographical research, writing the abstract, introduction, methodology, discussion, interpretation and description of results, conclusions, review and statistics. **Ana Paula Junqueira-Kipnis** contributed to project management, literature research, writing the abstract, introduction, methodology, discussion, interpretation and description of results, conclusions, review and statistics**. Jose Roberto Lapa e Silva** contributed to project administration, fund acquisition, bibliographic research, review and statistics**. Lia Gonçalves Possuelo** contributed to project management, bibliographic research, writing the abstract, introduction, methodology, discussion, interpretation and description of results, conclusions, review and statistics**. Ricardo Alexandre Arcêncio** contributed to project administration, bibliographical research, writing the abstract, introduction, methodology, discussion, interpretation and description of results, conclusions, review and statistics**.**

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ORIGINAL ARTICLE

Early sepsis in premature infants in Neonatal Intensive Care Units

Sepse precoce em prematuros de Unidades de Terapia Intensiva Neonatal

Sepsis temprana en bebés prematuros en Unidades de Cuidados Intensivos Neonatales

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Corresponding Author:
Raquel Cristina Gomes Lima
rcglima@gmail.com

Address: Rua Pastor Valdomiro Oliveira 455, apartamento 102. CEP: 45028-742 Bairro: Candeias. Vitória da Conquista-BA

Raquel Cristina Gomes Lima[1,2];
Danielle Souto de Medeiros[3];
Verônica Cheles Vieira[2,3];
Carla Silvana de Oliveira e Silva[4];

[1] *Universidade Estadual de Montes Claros, Montes Claros, MG, Brazil.*
[2] *Universidade Estadual do Sudoeste da Bahia, Vitória da Conquista, BA, Brazil.*
[3] *Instituto Multidisciplinar em Saúde, Universidade Federal da Bahia, Vitória da Conquista, BA, Brazil.*
[4] *Graduate Program in Health Sciences, Universidade Estadual de Montes, Montes Claros, MG, Brazil.*

ABSTRACT

Justification and Objectives: despite great advances in neonatal care, deaths in this age period remain high throughout the world, highlighting prematurity and neonatal sepsis as the main causes. This study aimed to assess the incidence of early neonatal sepsis and associated maternal and neonatal risk factors in premature infants admitted to Neonatal Intensive Care Units in a city in the countryside of Bahia. **Methods**: a non-concurrent cohort study including 268 preterm infants admitted on the day of birth between January 2016 and December 2017 and followed during the neonatal period. The incidence of early neonatal sepsis and its risk factors were calculated. Poisson regression with robust variance was used for multivariate analysis, obtaining estimates of Relative Risk (RR) and respective 95% Confidence Intervals (CI). Statistical significance was considered when p-value ≤ 0.05. **Results:** incidence of early sepsis was 38% (102), of which 12.3% (33) had sepsis treated by the clinic and 25.7% (69) also presented at least one laboratory alteration. The diagnosis of presumed early sepsis was identified in 63.4% (170); no sepsis was confirmed with culture; and sepsis was ruled out in 25.5% (68) of premature infants. The following were positively associated with the outcome: being born by vaginal delivery (RR: 1.53; 95%CI: 1.19-1.97), gestational age less than 32 weeks (RR: 1.86; 95%CI: 1.35-2.57), less than 28 weeks (RR: 2.16; 95%CI: 1.59-2.94) and 5-minute Apgar score less than 7 (RR: 1.45; 95%CI: 1.14-1.83). **Conclusion:** there was a high incidence of early sepsis compared with international and national research. The results suggest the need for strategies to prevent prematurity and improve care during childbirth.

Keywords: *Premature Newborn. Neonatal Sepsis. Neonatal Intensive Care Units. Longitudinal Studies.*

RESUMO

Justificativa e Objetivos*:* apesar dos grandes avanços na assistência neonatal, os óbitos nesse período etário continuam elevados em todo o mundo, destacando-se a prematuridade e a sepse neonatal como as principais causas. Este estudo objetivou *avaliar a incidência de sepse neonatal precoce e os fatores de risco materno e neonatal associados de prematuros internados nas Unidades de Terapia Intensiva Neonatais em uma cidade no interior da Bahia.* **Métodos:** estudo de coorte não concorrente, incluindo 268 prematuros internados no dia do nascimento, entre janeiro de 2016

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e dezembro de 2017, acompanhados no período neonatal. Foram calculados a incidência de sepse neonatal precoce e seus fatores de risco. Utilizou-se, para análise multivariada, a regressão de Poisson com variância robusta, obtendo-se estimativas do Risco Relativo (RR) e dos respectivos Intervalos de Confiança (IC) de 95%. Considerou-se significância estatística quando valor de p ≤ 0,05. **Resultados:** incidência da sepse precoce foi 38% (102), sendo que 12,3% (33) tiveram sepse tratada pela clínica e 25,7% (69) apresentaram, também, pelo menos uma alteração laboratorial. O diagnóstico de sepse precoce presumida foi identificado em 63,4% (170); nenhuma sepse foi confirmada com cultura; e a sepse foi afastada em 25,5% (68) dos prematuros. Associaram-se positivamente ao desfecho nascer de parto vaginal (RR: 1,53; IC95%: 1,19-1,97), idade gestacional menor que 32 semanas (RR: 1,86; IC95%: 1,35-2,57), menor que 28 semanas (RR: 2,16; IC95%: 1,59-2,94) e Apgar 5º minuto menor que 7 (RR: 1,45; IC95%:1,14-1,83). **Conclusão:** houve elevada incidência de sepse precoce, comparada com as pesquisas internacionais e nacionais. Os resultados sugerem necessidade de estratégias para a prevenção da prematuridade e melhoria da assistência durante o parto.

Descritores: *Recém-Nascido Prematuro. Sepse Neonatal. Unidades de Terapia Intensiva Neonatal. Estudos Longitudinais.*

RESUMEN

Justificación y Objetivos: a pesar de los grandes avances en la atención neonatal, las muertes en este período de edad siguen siendo elevadas en todo el mundo, destacando la prematuridad y la sepsis neonatal como principales causas. Este estudio tuvo como objetivo evaluar la incidencia de sepsis neonatal temprana y factores de riesgo maternos y neonatales asociados en bebés prematuros ingresados en Unidades de Cuidados Intensivos Neonatales en una ciudad del interior de Bahía. **Métodos**: estudio de cohorte no concurrente, que incluyó 268 prematuros hospitalizados el día del nacimiento, entre enero de 2016 y diciembre de 2017, seguidos en el período neonatal. Se calculó la incidencia de sepsis neonatal temprana y sus factores de riesgo. Para el análisis multivariado se utilizó la regresión de Poisson con varianza robusta, obteniendo estimaciones del Riesgo Relativo (RR) y los respectivos Intervalos de Confianza (IC) del 95%. Se consideró significación estadística cuando el valor de p ≤ 0,05. **Resultados**: La incidencia de sepsis temprana fue del 38 % (102), el 12,3 % (33) recibió tratamiento de sepsis en la clínica y el 25,7 % (69) también tuvo al menos una anomalía de laboratorio. El diagnóstico de presunta sepsis temprana se identificó en el 63,4% (170); no se confirmó sepsis con cultivo; y se descartó sepsis en el 25,5% (68) de los bebés prematuros. Se asociaron positivamente con el resultado de nacer por vía vaginal (RR: 1,53; IC95%: 1,19-1,97), edad gestacional menor de 32 semanas (RR: 1,86; IC95%: 1,35-2,57), menos de 28 semanas (RR: 2,16; IC95%: 1,59-2,94) y Apgar al quinto minuto inferior a 7 (RR: 1,45; IC95%: 1,14-1,83). **Conclusión**: hubo una alta incidencia de sepsis temprana, en comparación con la investigación nacional e internacional. Los resultados sugieren la necesidad de estrategias para prevenir la prematuridad y mejorar la atención durante el parto.

Palabras Clave: *Recién Nacido Prematuro. Sepsis Neonatal. Unidades de Cuidados Intensivos Neonatales. Estudios Longitudinales.*

INTRODUCTION

In Brazil, despite the downward trend in infant mortality in recent years, a slow reduction in the early neonatal component has been observed, with 1/5 of deaths occurring on the first day of life and the majority of causes considered preventable when adequate attention is provided to women's and newborns' health.[1] Investigation of this component highlights neonatal sepsis as one of the main causes of these deaths, especially in premature and very low birth weight newborns.[2,3]

Early-onset neonatal sepsis is characterized as a clinical syndrome with systemic signs of infection that occurs in the first 72 hours of life, originating from bacterial pathogens transmitted vertically from mother to newborn before or during delivery.[4,5] The microorganisms most involved in its pathogenesis are group B *Streptococcus* (GBS), *Escherichia coli* and *Listeria monocytogenes*, which together account for approximately 65% to 70%, respectively, of all systemic neonatal bacterial diseases.[6]

The incidence of culture-proven early-onset sepsis in the United States from 2005 to 2008 ranged from 0.75 to 0.77 cases/1,000 live births, and mortality was 10.9%. Black preterm infants had higher rates (5.14 cases/1,000 live births), and 24.4% died.[7] Research at the Vermont Oxford Network, from 2007 to 2016, identified 3.7% of early sepsis in extremely premature infants.[8] In the *Rede Brasileira de Pesquisas Neonatais* (RBPN, Brazilian Neonatal Research Network), from 2006 to 2017, the prevalence of this sepsis was 15.5 cases/1,000 very low birth weight newborns, and 52.9% evolved to death.[2]

"Suspected" early neonatal sepsis is one of the most common and challenging diagnoses in Neonatal Intensive Care Units (NICUs), given that the signs and symptoms may be minimal or nonspecific and confused with clinical conditions typical of birth and adaptation to the extrauterine environment, especially in premature infants.[2,9] Therefore, there is a great challenge for healthcare professionals in identifying newborns with a high probability of early sepsis and initiating antimicrobial therapy as well as discontinuing this therapy when infection is considered unlikely.[10]

Several risk factors are involved in the genesis of early sepsis, being grouped into maternal or neonatal factors, highlighting premature labor, rupture of amniotic membranes 18 hours or more before delivery, chorioamnionitis, maternal colonization by EGB, maternal fever during or immediately after delivery,[11] premature newborns with low 5-minute Apgar scores and need for resuscitation at birth.[12,13]

Most studies on this topic are concentrated in large centers, mainly in university hospitals, where research and prophylaxis for GBS in pregnant women are routinely carried out, and neonatal units have strict management for carrying out cultures and using antimicrobial agents, which does not occur in most maternal and child hospitals in the countryside of Brazil. Little is known about the true incidence of early neonatal sepsis in low- and middle-income countries.[14] Therefore, this research aims to assess the incidence of early neonatal sepsis, the associated maternal and neonatal risk factors and the evolution of premature infants admitted to three NICUs in a city in the countryside of Bahia.

METHODS

This is a non-concurrent, hospital-based cohort study, including premature infants admitted to the three NICUs on the first day of life, from January 1, 2016 to December 31, 2017. The research was carried out in the city of Vitória da Conquista, the third largest city in the state of Bahia, headquarters of the Southwest Regional Health Center.

The study population was monitored until 27 days of life. Since this was a larger study, the exclusion criterion was being premature with a congenital anomaly (complex congenital heart disease, gastrointestinal tract atresia, abdominal wall defects, hydrocephalus, encephalocele and diaphragmatic hernia).

The data were obtained by analyzing medical records stored in the medical and statistical archive service of the three hospitals. NICUs have ten beds each, two of which are located in public hospitals and the other in a private hospital.

The sample was obtained by convenience (n=268). However, the smallest sample size necessary to represent the population of premature infants in the region was estimated at 120, considering the following parameters: infinite population size (given that it is not possible to estimate the total number of premature infants who would require neonatal intensive care); expected frequency of early neonatal sepsis of 8.5%, according to Barbosa *et al*. (2014), in Uberlândia;[15] 5% accuracy; and 95% Confidence Interval.

Data were obtained through a specific questionnaire based on the Birth Survey for Brazil[3] instrument by volunteer health researchers, after training and under the supervision of neonatologists. The main fieldwork took place from June 2018 to April 2019, using a digital questionnaire through the Kobo Toolbox 1.4.8® software.

The dependent variable was early neonatal sepsis. The diagnostic description in medical records and the use of an empirical therapeutic regimen of ampicillin or crystalline penicillin G associated with gentamicin (protocol in the units) in the first 72 hours of life were considered.

Sepsis was categorized as presumed early-onset neonatal sepsis (PES) when clinical signs and symptoms compatible with the disease occurred, and an antimicrobial regimen was initiated. Confirmed early-onset neonatal sepsis (CNS) was considered if a positive blood culture was obtained. PES was divided into rule out neonatal sepsis (RNS), whose clinical and laboratory evolution allowed the suspension of antibiotics within four days, and treated neonatal sepsis (TNS), which were those who received the antimicrobial regimen between five days and more.[16]

Within the TNS group, a subdivision was made into clinically treated neonatal sepsis (CTNS) and clinically treated neonatal sepsis with at least one laboratory alteration (CTNSL). According to Procianoy *et al*. (2020), the number of leukocytes above 25,000 or below 5,000 and the immature neutrophil to total ratio (I/T) above 0.2 or C-reactive protein above 10.[17] The death certificates of premature infants with PES who died in the first four days of life were assessed. When the declared cause was early neonatal sepsis or septic shock, the TNS category was assigned to those who had been treated for less than four days. For these premature infants, a sensitivity analysis was performed by comparing the results of the analyses, including these premature infants in the group described above and excluding them from the analyses for subsequent decision-making.

For these premature infants, a sensitivity analysis was performed to compare the results obtained from the decision to include deaths in the category described above and exclude them from the analysis.

In cases of suspected early sepsis, it was routine in the three units to collect a blood culture sample before starting antimicrobial agents. Microorganism isolation was performed using the manual or automated blood culture method in the three units by an outsourced laboratory.

The independent variables analyzed were divided into two chunks. Chunk I contained maternal demographic characteristics, maternal morbidities, and prenatal and delivery care. The variables used were maternal age (<20 years, ≥20 years), marital status (with partner and without partner), preterm labor (no or yes), hypertensive syndrome (no or yes), number of prenatal consultations (up to five consultations or six and more consultations), and type of delivery (cesarean or vaginal).

Chunk II included the characteristics of premature infants, neonatal care received and clinical evolution, such as the sex of premature infants (male or female), estimated gestational age in weeks, categorized as extremely premature (less than 28 weeks), very premature (28 to less than 32 weeks) and moderate/late premature (32 to less than 37 weeks). Birth weight was measured in grams and divided into ≥ 1,500 g or < 1,500 g, 5th-minute Apgar (< 7 or ≥ 7), hypothermia on admission to the NICU (no or yes). Clinical outcomes were assessed through the diagnosis of late neonatal sepsis and neonatal death, both categorized as no or yes.

In order to obtain information regarding the missing medical records, the nursing admission books of the NICUs were analyzed. The assessment of losses was made by comparing the sample obtained with the total population using Pearson's chi-square test or linear trend.

Initially, a descriptive analysis of the variables studied was performed, presenting absolute and relative frequencies. All variables were also described according to the categories of early neonatal sepsis, such as absent, ruled out and treated (CTNS and CTNSL), compared using Pearson's chi-square test or Fisher's exact test. Sensitivity analysis was performed using Pearson's chi-square test.

For the bivariate analysis, the early neonatal sepsis variable was recategorized as absent and treated (CTNS and CTNSL). The RNS category was removed from the analyses due to its behavior being different from the other sepsis categories (absent or TNS) and the insufficient number of observations for an analysis as an isolated category. The assessment of the progression to late neonatal sepsis and death was performed according to the groups of absent and treated early neonatal sepsis. Bivariate analysis between independent variables and treated early neonatal sepsis was performed using Poisson Regression with robust variance, obtaining estimates of the unadjusted Relative Risk ($_u$RR) and their respective 95% Confidence Intervals (95%CI).

For multivariate analysis, the independent variables from chunks I and II were used, which met the following criteria: p-value ≤ 20% (by the Wald test); loss of less than 10%; and the assumption of independence between variables. The models were compared by the Akaike criterion, and adequacy was assessed by the chi-square test. For all tests and for the permanence of the variables in the final model, a p-value ≤ 0.05 was used. The Stata, version 15.1 (Stata Corporation, College Station, USA), was used for data analysis.

This research was carried out taking into account the guarantee of ethical and legal principles that govern research on human beings, recommended in Resolutions 466/2012, 510/2016 and 580/2018 of the Ministry of Health, approved by the Research Ethics Committee, with *Certificado de Apresentação para Apreciação Ética* (CAAE, Certificate of Presentation for Ethical Consideration) 42401920.0.0000.5049, on February 5, 2018.

RESULTS

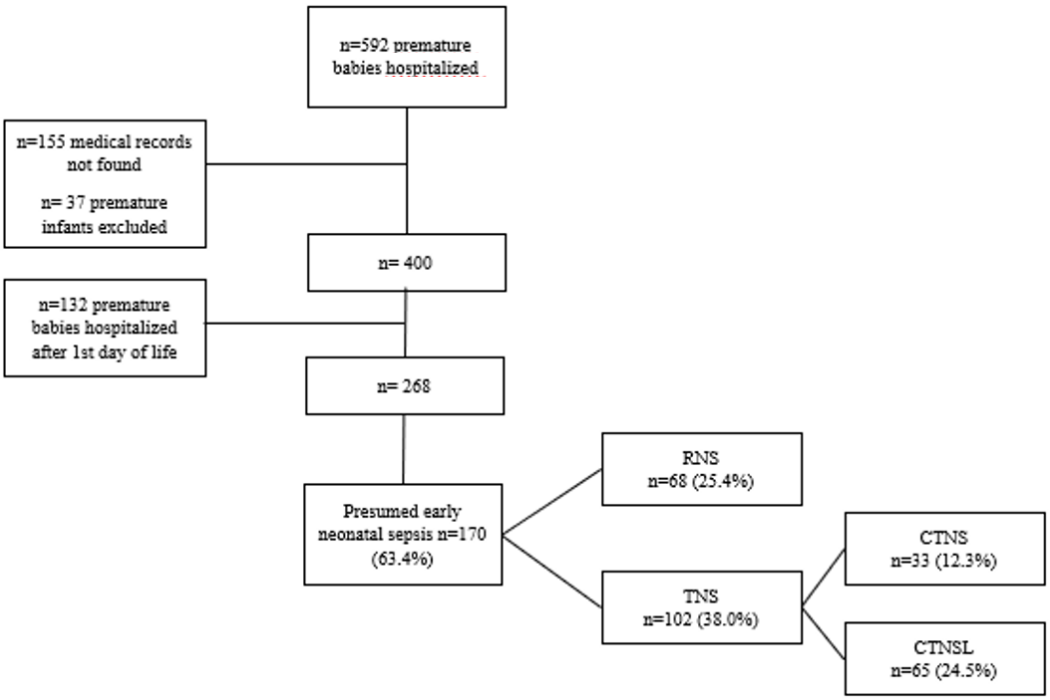
During the two years of study, 592 premature infants were admitted to the NICUs, 37 of whom were excluded due to congenital malformations, and 155 medical records were not located, leaving a sample of 400 premature infants. Medical records that were not located were assessed as possible losses. No differential loss was observed, and the use of calibration factors was not necessary to conduct the other analyses. The following variables were analyzed: hospital of origin (p=0.261); birth weight (p=0.917); gestational age (p=0.948); death (p=0.939); and according to 2016 and 2017 (p=0.827).

For the present study, 268 premature infants were included. Concerning maternal characteristics, most mothers were over 20 years old, lived without a partner and evolved to cesarean delivery. In relation to the characteristics of premature infants and neonatal care, the majority were male, classified as moderate/late premature, weighed over 1,500 g, had a 5-minute Apgar score greater than or equal to 7 and were hypothermic upon admission to the NICU (Table 1).

Table 1. Description of the characteristics of the premature population (n=268). Vitória da Conquista, BA, Brazil, 2016/2017.

Variables	N	%
Mother's age		
< 20 years	44	16.4
≥ 20 years	224	83.6
Mother's marital status		
With partner	113	46.5
Without partner	130	53.5
Premature labor		
No	130	50.2
Yes	129	49.8
Hypertensive syndrome		
No	179	66.8
Yes	89	33.2
Number of prenatal consultations		
Up to 5	118	50.0
6 and more	118	50.0
Type of delivery		
Caesarean section	193	72.3
Vaginal	74	27.7
Sex		
Male	143	53.4
Female	125	46.6
Gestational age at birth		
Moderately premature/late premature	166	61.9
Very premature	67	25.0
Extremely premature	35	13.1
Birth weight		
≥ 1,500g	163	60.8
< 1,500g	105	39.2
5-minute Apgar		
≥7	232	88.2
< 7	31	11.8
Hypothermia on admission to the Neonatal Intensive Care Unit		
No	67	32.7
Yes	138	67.3
Late neonatal sepsis		
No	205	76.5
Yes	63	23.5
Neonatal death		
No	232	86.6
Yes	36	13.4

Note: authors according to Coorte Nascer Prematuro, 2016/2017.



Note: authors according to Coorte Nascer Prematuro, 2016/2017.

Figure 1. Premature infants admitted to Neonatal Intensive Care Units and their distribution according to evolution, such as ruled out neonatal sepsis, neonatal sepsis treated, neonatal sepsis treated due to clinical alterations, neonatal sepsis treated due to clinical alterations and at least one laboratory alteration.

Fourteen premature deaths were recorded before 4 days of life, of which nine had early sepsis or septic shock as the cause of death (death certificate). These patients were removed from the RNS group and included in the CTNS or CTNSL groups. To perform a sensitivity assessment, the analyses were repeated excluding these nine newborns, and no differences were observed between the results. It was therefore decided to keep them in the analyses.

A total of 170 (63.4%) (95%CI: 57.4-69.0) premature infants had PES, of which 68 (25.4%) (95%CI: 20.4-30.9) had RNS and 102 (38.0%) (95%CI: 32.4-44.0) had TNS. Of the total number of premature infants in the study (268), 33 (12.3%) (95%CI: 8.8-16.8) had CTNS, and 65 (24.5%) (95% CI: 20.8-31.3) had CTNSL (Figure 1).

When comparing the groups and the variables of chunks I and II, it was found that there is an association between maternal age (p=0.008), hypertensive syndrome (p=0.014), premature labor (p=0.013), type of delivery (p<0.001), gestational age at birth (p<0.001), birth weight (p<0.001) and 5-minute Apgar (p=0.001) (Table 2).

The bivariate analysis of the variables in chunk I demonstrated a higher risk for TNS in mothers under 20 years of age, who lived without a partner, who developed premature labor and who had a vaginal delivery. And a protective factor for the outcome included mothers with some hypertensive syndrome during pregnancy and who had six or more prenatal consultations. Regarding the variables in chunk II, a positive association, gestational age less than 32 weeks, birth weight less than 1,500 g and 5-minute Apgar score less than 7 were evidenced.

The variables maternal age, hypertensive syndrome during pregnancy, type of delivery, gestational age, birth weight and 5-minute Apgar met the adopted criteria and were included as a chunk in the multivariate analysis. After adjustment, being born by vaginal delivery, with a gestational age of less than 32 weeks and a 5-minute Apgar score of less than 7 remained significantly associated with the outcome (Table 3).

Late-onset neonatal sepsis and neonatal death occurred in 41 (40.2%) and 25 (24.5%) premature infants, respectively, who had TNS. The two conditions analyzed were significantly associated with the outcome (Table 4).

Table 2. Distribution of variables from chunks I and II according to the following groups of early neonatal sepsis, as absent, ruled out, treated with clinical alterations and treated with clinical and laboratory alterations, p value (n=268). Vitória da Conquista, BA, Brazil, 2016/2017.

	Absent		Rule out early neonatal sepsis		Early neonatal sepsis treated				p-value*
					With clinical changes		With clinical and laboratory changes		
	N	%	N	%	N	%	N	%	
Age									0.008
< 20 years	7	15.9	18	40.9	5	11.4	14	31.8	
≥ 20 years	91	40.6	50	22.3	28	12.5	55	24.6	
Marital status									0.080
With partner	51	45.1	27	23.9	11	9.7	24	21.3	
No partner	38	29.2	37	28.5	18	13.8	37	28.5	
Hypertensive syndrome									0.014
No	55	30.7	54	30.2	21	11.7	49	27.4	
Yes	43	48.3	14	15.7	12	13.5	20	22.5	
Prenatal consultations									0.077
Up to 5	36	30.5	33	28.0	15	12.7	34	28.8	
6 and more	55	46.6	28	23.7	12	10.2	23	19.5	
Premature labor									0.013
No	59	45.4	32	24.6	10	7.7	29	22.3	
Yes	36	27.9	34	26.4	21	16.3	38	29.4	
Type of delivery									< 0.001
Caesarean section	90	46.6	47	24.4	17	8.8	39	20.2	
Vaginal	8	10.8	21	28.4	16	21.6	29	39.2	
Sex									0.087
Male	51	35.6	43	30.1	12	8.4	37	25.9	
Female	47	37.6	25	20.0	21	16.8	32	25.6	
Gestational age									< 0.001
Moderate/late preterm	84	50.6	41	24.7	11	6.6	30	18.1	
Very premature	12	17.9	17	31.3	15	19.4	23	31.4	
Extremely premature	2	5.7	10	28.6	7	20.0	16	45.7	
Birth weight									< 0.001
≥ 1,500 g	77	47.2	44	27.0	11	6.7	31	19.0	
< 1,500 g	21	20.0	24	22.9	22	20.9	30	36.2	
5-minute Apgar									0.001
≥7	94	40.5	59	25.4	18	7.8	61	26.3	
< 7	4	12.9	7	22.6	12	38.7	8	25.8	
Hypothermia on admission									0.606
No	26	38.8	19	28.4	8	11.9	14	20.9	
Yes	55	39.9	29	21.0	16	11.6	38	27.5	

*Note: *Pearson's chi-square test or Fisher's exact test.*

Table 3. Result of bivariate and multivariate analysis between the independent variables of chunk I and II and treated neonatal sepsis, unadjusted and adjusted relative risk with their respective 95% confidence intervals (n = 200). Vitória da Conquista – BA, 2016/2017.

Variables	Unadjusted RR	95%CI	Adjusted RR	95%CI
Mother's age				-
≥ 20 years	1.00		-	-
< 20 years	1.53	1.15-2.02	-	
Mother's marital status				
With partner	1.00	-		
No partner	1.45	1.06-1.97		
Premature labor				
No	1.00	-		
Yes	1.56	1.16-2.08		
Hypertensive syndrome				-
No	1.00	-	-	-
Yes	0.76	0.56-1.03	-	
Number of prenatal consultations				
Up to 5	1.00	-		
6 and more	0.67	0.49-0.92		

Type of delivery				-
Caesarean section	1.00	-	1.00	1.19-1.97
Vaginal	2.21	1.74-2.80	1.53	
Sex				
Male	1.00	-		
Female	1.08	0.82-1.42		
Gestational age				-
Moderate/late preterm	1.00	-	1.00	1.35-2.57
Very premature	2.31	1.72-3.11	1.86	1.59-2.94
Extremely premature	2.80	2.12-3.69	2.16	
Birth weight				-
≥ 1,500 g	1.00	-	-	-
< 1,500 g	2.09	1.59-2.76	-	
5-minute Apgar				-
≥7	1.00		1.00	1.14-1.83
< 7	1.82	1.43-2.32	1.45	
Hypothermia on admission				
No	1.00	-		
Yes	1.08	0.75-1.55		

Note: RR: relative risk; 95%CI: 95% Confidence Interval.

DISCUSSION

This study demonstrates the difficulties faced in the management of early neonatal sepsis in premature infants, in which it was found that most of them had clinical signs and symptoms that motivated the introduction of antimicrobial agents. As a result of rigorous clinical and laboratory monitoring, it was possible to suspend antibiotics in 25.4% of cases. Different results were verified by the RBPN, in which 74.3% of premature infants did not require antibiotics in the first 48 hours of life, and it was possible to interrupt them in 44% of cases within 48-72 hours. This demonstrates the impact of the strategies used in the institution for the rational use of antimicrobial agents.[2]

Despite the routine collection of blood cultures in units before starting antibiotics, no positive culture results were detected, making diagnostic accuracy more difficult. Obtaining insufficient blood volume (due to prematurity) and the absence of automated systems (due to a lack of vials in public services) in all cultures may have influenced the results. No similar results were identified in this cohort. International and national studies demonstrate low culture positivity in early neonatal sepsis, being 5.93% in India (2017),[18] 2.9% in Uberlândia (2011)[15] and 1.3% in Campinas (2006-2017).[2]

It was found that 12.3% of premature infants treated did not have any laboratory abnormalities identified and were treated based on clinical manifestations. This is the difficulty in achieving diagnostic accuracy, since the signs and symptoms may be minimal or nonspecific and confused with other non-infectious inflammatory syndromes, and diagnostic tests have a low positive predictive value. Therefore, the decision to treat a newborn also depends on other factors, such as the presence of maternal risk factors, the frequency of observations and the degree of prematurity of newborns.[2,9,10]

The incidence of early sepsis in this cohort was similar to that observed in public hospitals in Ethiopia in 2019 (38%),[13] but high when compared with other studies. In England, the incidence in extremely premature infants (2007-1016) was 3.7%.[8] In Brazil, in 2011, 8.5% of newborns presented the aforementioned outcome.[15]

It is worth highlighting the methodological differences found in several studies on this topic. Some studies only include CNS through culture, others include all neonates, which made the comparative aspect difficult. Also regarding the calculation of the incidence of sepsis, most sources demonstrate the rates for every 1,000 live births.

In this cohort, being born vaginally remained an independent factor for early sepsis. This finding was also evidenced in other studies.[12,19] This type of delivery may be associated with prolonged rupture of the amniotic membranes (> 18 hours), chorioamnionitis or exposure to GBS[11,13]. In this cohort, being born at a gestational age of less than 32 weeks was associated with an increased risk of early sepsis, which can be supported by several international and national studies.[2,10,13,20,21] It is known that premature infants present immunological dysfunction due to the absence of maternal transplacental transfer of IgG, immature cellular responses, and deficiencies of soluble proteins and peptides.[21]

Being born with a 5-minute Apgar score of less than 7 led to a 45% higher risk of early-onset sepsis. Similar results were found in public hospitals in southern Ethiopia.[12] This association can be explained by the fact that perinatal asphyxia causes an immunological insult, contributing to a worsening of the response to combat infections in premature infants who already have an impaired innate immune status.[11, 22]

It was found that premature infants with early neonatal sepsis had a 6.5 and 12.0 times greater risk of developing late-onset sepsis and neonatal death, respectively. These findings support the research conducted by the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network, which followed premature infants treated for early-onset sepsis. The presence of this diagnosis was associated with late-onset sepsis, necrotizing enterocolitis and death.[23]

Following the Ministry of Health recommendations, there is no routine screening for GBS in prenatal care provided by the Unified Health System in this region.[24] This contributes to the lack of knowledge about the prevalence of colonization of pregnant women by this agent combined with the negativity of all blood cultures, which led to difficulties in identifying the microorganisms responsible for sepsis. In order to clarify this gap, a pioneering study carried out in this city screened GBS in pregnant women and identified a prevalence of 18.1%, highlighting the importance of implementing this routine in prenatal care practices in the public health system.[25]

Among the limitations of this study, retrospective design with possible information bias, in addition to not obtaining some important maternal variables for the outcome studied, such as time of rupture of amniotic membranes, status of colonization by EGB, use of antimicrobial agents by the mother and diagnosis of chorioamnionitis, stood out.

Early-onset neonatal sepsis is one of the main diagnoses in NICUs. Its management is also one of the greatest challenges in neonatology, given that the clinical signs and symptoms are nonspecific, especially in premature infants, and can be confused with non-infectious conditions, combined with the low sensitivity of laboratory tests. In this cohort, a high incidence of TNS was identified, with most premature infants requiring antibiotics after birth and no microorganisms being isolated in blood cultures. The independent risk factors for early-onset neonatal sepsis include being born by vaginal delivery, with a gestational age of less than 32 weeks and a 5-minute Apgar score below 7. Furthermore, early-onset sepsis behaved as a risk factor for late-onset neonatal sepsis and death. These findings demonstrate the need to improve the quality of prenatal care, strategies to prevent prematurity, and management during birth to avoid perinatal asphyxia.

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AUTHORS' CONTRIBUTIONS

Raquel Cristina Gomes Lima contributed to project administration, literature search, abstract writing, introduction, methodology, discussion, interpretation and description of results, preparation of tables, conclusions, review and statistics**. Danielle Souto de Medeiros** contributed to project administration, literature search, abstract writing, introduction, methodology, discussion, interpretation and description of results, preparation of tables, conclusions, review and statistics. **Verônica Cheles Vieira** contributed to abstract writing, methodology, interpretation of results, conclusions, review and statistics. **Carla Silvana de Oliveira e Silva** contributed to the literature search, abstract writing, introduction, methodology, discussion, interpretation and description of results, conclusions, review and statistics.

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

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ORIGINAL ARTICLE

Spatial epidemiological approach to tuberculosis in Pernambuco

Abordagem epidemiológica espacial da tuberculose em Pernambuco

Abordaje epidemiológico espacial de la tuberculosis en Pernambuco

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Corresponding Author:
Gisele Matias de Freitas
gisele.matiasf@gmail.com

Address: Av. Moraes Rego, s/n, Campus da UFPE - Cidade Universitária - Recife/PE - CEP: 50670-420.

Gisele Matias de Freitas[1];
Louisiana Regadas de Macedo Quinino[2];
Flávia Helena Manhães de Vasconcellos[1];
Isabel Soares Diniz Oliveira[1];

[1] *Universidade Federal de Pernambuco, PE, Brazil.*
[2] *Instituto Aggeu Magalhães (Fiocruz) Researcher, PE, Brazil.*

ABSTRACT

Background and Objectives: Pernambuco is among the states with the highest detection and mortality rates for tuberculosis, a disease directly related to social and health inequalities. We proposed to analyze the epidemiological characteristics of tuberculosis from 2011 to 2020 in the health macroregions of Pernambuco. **Methods:** this was an ecological study of notified cases of tuberculosis confirmed in the macroregions of the state of Pernambuco between 2011 and 2020. The behavior of tuberculosis in Pernambuco over time and space was analyzed. **Results:** there were 56,700 confirmed cases of tuberculosis per municipality of residence in Pernambuco during the study period. The overall average detection rate for the period was 35.6/100,000 inhabitants, with the highest rate recorded in macroregion 1, with 58.45 cases/100,000 inhabitants, and the lowest in macroregion 3, with 19.74 cases/100,000 inhabitants. The results show an increase in the concentration of cases in the state's Metropolitan Region. **Conclusion:** tuberculosis control requires contextual actions to improve people's general living conditions. Social support is aimed at socially vulnerable people in general, and there is no specific support for this public.

Keywords: *Tuberculosis. Epidemiology. Social Determinants of Health. Space-Time Analysis.*

RESUMO

Justificativa e Objetivos: Pernambuco está entre os estados com maiores coeficientes de detecção e mortalidade por tuberculose, doença diretamente relacionada às iniquidades social e de saúde. Propõe-se analisar as características epidemiológicas da tuberculose no período de 2011 a 2020 nas macrorregiões de saúde de Pernambuco. **Métodos:** estudo ecológico que considerou os casos notificados confirmados para tuberculose nas macrorregiões do estado de Pernambuco entre 2011 e 2020. Analisou-se o comportamento da tuberculose em Pernambuco no tempo e no espaço. **Resultados:** houve um registro de 56,7 mil casos confirmados de tuberculose por município de residência em Pernambuco no período do estudo. A média geral da taxa de detecção no período foi de 35,6/100

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mil habitantes, sendo a maior taxa registrada na macrorregião 1, com 58,45 casos/100 mil habitantes, e a menor, na macrorregião 3, com 19,74 casos/100 mil habitantes. Os resultados mostram aumento na concentração de casos na Região Metropolitana do estado. **Conclusão:** o controle da tuberculose necessita de ações contextuais, no sentido de melhorar a condição geral de vida das pessoas. O suporte social é destinado às pessoas em vulnerabilidade social no geral, não havendo suporte específico a esse público.

Descritores:*Tuberculose. Epidemiologia. Determinantes Sociais da Saúde. Análise Espaço-Temporal.*

RESUMEN

Justificación y Objetivos: Pernambuco se encuentra entre los estados con mayores tasas de detección y mortalidad por tuberculosis, enfermedad directamente relacionada con las desigualdades sociales y sanitarias. El objetivo es analizar las características epidemiológicas de la tuberculosis entre 2011 y 2020 en las macrorregiones sanitarias de Pernambuco. **Métodos:** estudio ecológico que analizó los casos notificados confirmados de tuberculosis en las macrorregiones del estado de Pernambuco entre 2011 y 2020. Se analizó el comportamiento de la tuberculosis en Pernambuco en tiempo y en espacio. **Resultados:** hubo 56.700 casos confirmados de tuberculosis por municipio de residencia en Pernambuco durante el período de estudio. La tasa media global de detección en el período fue de 35,6/100.000 habitantes, registrándose la tasa más alta en la macrorregión 1, con 58,45 casos/100.000 habitantes, y la más baja en la macrorregión 3, con 19,74 casos/100.000 habitantes. Los resultados muestran un aumento de la concentración de casos en la región metropolitana del estado. **Conclusión:** el control de la tuberculosis requiere acciones contextuales para mejorar las condiciones generales de vida de las personas. El apoyo social está dirigido a las personas socialmente vulnerables en general, y no hay apoyo específico para este público.

Palabras Clave: *Tuberculosis. Epidemiología. Los Determinantes Sociales de la Salud. AnálisisEspacio-Temporal.*

INTRODUCTION

Tuberculosis (TB) is a chronic infectious disease that persists with high prevalence in Brazil and worldwide, and is the leading cause of death from a single infectious agent. In 2020, 10.6 million people were infected with TB and more than one million people died from the disease worldwide.

Brazil is the only country in the Americas present on two lists of priority countries for the World Health Organization (WHO) (TB and TB-Human Immunodeficiency Virus (HIV)).[1] The Ministry of Health epidemiological bulletin reveals that Brazil remains among the 30 countries with the most cases of TB and TB-HIV co-infection, becoming a priority for disease control according to theWHO. In 2020, 66,819 new cases were reported, generating an incidence coefficient of 31.6 cases per 100,000 inhabitants and approximately 4,500 deaths from the disease were recorded, reaching 2.2 deaths per 100,000 inhabitants, considering the country's capitals.[2]

Pernambuco is among the states with the highest incidence and mortality rates for TB. The capital, Recife, has the second highest incidence rate among Brazilian capitals, at 106 per 100,000 inhabitants, behind only Manaus, which has a rate of 114/100,000 inhabitants. This pattern in the distribution of TB in Brazil, centered on Metropolitan Regions, is related to the persistence of peripheral urban areas, whose characteristics include the presence of low-income populations and less access to basic services and infrastructure. Moreover, the periphery is often marked by a lack of public investment and the presence of social problems, such as violence and lack of job opportunities, which favor the spread of the disease.[3]

TB is therefore a socially determined disease, directly related to poverty, inequality and social exclusion, which in turn will influence people's health status. Social vulnerability exposes individuals to greater contact with the etiological agent and subsequent illness due to nutritional deficiency, lack of basic health services and precarious working and housing conditions. As it is a disease of great proportions, it is observed that it has a strong influence in poorer countries and in the outskirts of metropolitan areas, which justifies the high incidence in countries with a low Human Development Index (HDI).[4]

The lack of access to information, resulting from low levels of education and failure to promote health, increases the number of cases of the disease. Low levels of education can negatively influence the understanding of the importance of correct treatment and the risks of abandoning the therapeutic process, creating obstacles to controlling this disease and thus contributing to the emergence of new strains resistant to anti-TB drugs.[5]

Considering TB characteristics, it is important to understand it from the perspective of One Health. This approach considers the interconnections between human, animal and environmental health, bringing an interdisciplinary view and their interactions over time. The One Health approach is becoming an essential concept for public policy makers seeking strategies for more efficient administration and better governance. However, few of them cover all the pillars of the approach to prevent diseases, protect and promote health, due to the low importance given to the institutional, political and social factors associated with a One Health approach.[6]

The COVID-19 pandemic has had a significant impact on TB numbers. Due to difficulties in accessing services, the number of people affected by TB worldwide fell from a peak of 7.1 million in 2019 to 5.8 million in

2020 (-18%), returning to the 2012 level. This scenario shows that the number of people with undiagnosed and untreated TB has increased, resulting in higher TB deaths and increased community transmission of the infection.[7]

The term "syndemic" is suggested to explain the harmful interaction between TB and COVID-19, given that the aforementioned social, economic and environmental contexts, which determine populations'living conditions, enhance the interaction between coexisting diseases and the excessive burden of the resulting consequences.[8]

The aim is to understand the epidemiological aspects of this disease in Pernambuco in the pre-pandemic period, focusing on spatial and temporal approaches, aiming to identify characteristics present in certain areas that may influence the expression of the TB incidence coefficient before the influence of the pandemic.

METHODS

This is an ecological study that considered all confirmed cases of TB reported in the state of Pernambuco from 2011 to 2020.

Pernambuco is one of the most unequal states in Brazil in terms of income concentration. It has a Gini Index (per capita household income) of 0.62, with the smallest municipality showing 0.47, and the largest, 0.63, with the lowest values detected in the municipalities of the countryside (rural area). With the HDI, the opposite happens: the municipalities of the Metropolitan Region of Recife (MRR) have the highest values, with the index varying from 0.48 to 0.78. The state has an HDI of 0.72. The inequality map of Brazilian capitals published in 2019 points to Recife as the most unequal among the capitals. Moreover, the state is in third place in income concentration.[9]

In compliance with the principle of decentralization of health actions proposed by the Brazilian Health System (In Portuguese, *Sistema Único de Saúde* - SUS), Pernambuco is subdivided into four Interstate Health Macroregions (IHM): Metropolitan Region; *Agreste*; *Sertão*; and *Vale do São Francisco* and *Araripina* (Figure 1). These territorial arrangements bring together more than one health region, with the aim of agreeing on interregional actions, services and interests, constituting an example of coordination at various levels beyond borders.[10]

The data was extracted from the SUS Information Technology Department (In Portuguese, *Departamento de Informática do SUS*- DATASUS) (datasus.saude.gov.br).[11] All confirmed TB cases residing in the state of Pernambuco between 2011 and 2020 were included in the study. The selections used were "confirmed TB cases", "year of notification", "municipality of residence" and "Macrorreg.Saúde/Munic.de resid" in the period 2011-2020. Cases outside the investigation period, with incomplete or missing data and cases of drug-resistant

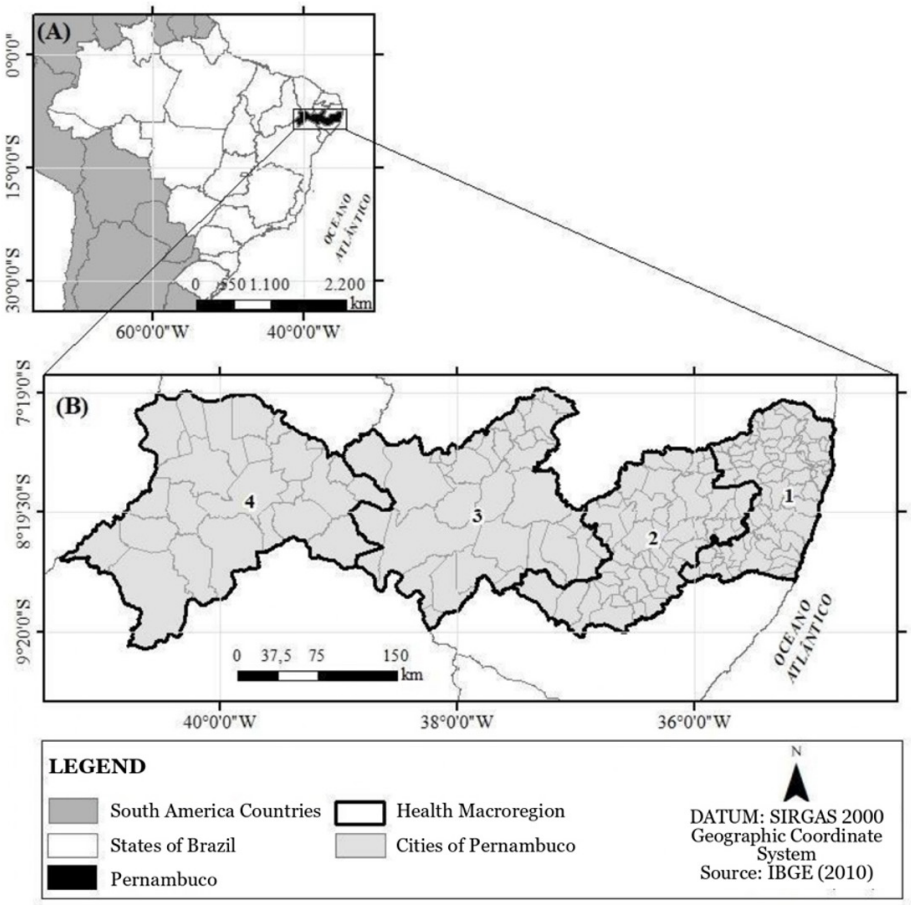


Figure 1. Map of the state of Pernambuco, Brazil, highlighting its four health macroregions.

TB were excluded from the study.

In order to differentiate the macroregions (MR) in relation to socioeconomic characteristics, a table was created with data on population density, Gini index, urbanization rate and number of commercial buildings.

The absolute number of TB cases per municipality and state was addressed as well as the TB detection rate according to its spatial distribution. For comparative purposes, the information was considered for five-year periods (2011-2015 and 2016-2020). Instead of the traditional nomenclature "incidence coefficient", this article chose to use the "detection rate", considering that the chronicity of TB cases does not allow for a true incidence, since it is not known when a patient became infected. However, there is no difference between the calculation methods.

The detection rate calculation was obtained using the formula:

$$\frac{\text{Number of TB cases reported in Pernambuco between 2011-2020}}{\text{Mid-period adjusted population x 10n}}$$

For the temporal approach, descriptive statistics of detection rates by MR and for the state were presented in tables, considering the total study period and each five-year period.

In order to verify the behavior of the response variable in space, the incidence rate was initially distributed by municipality, classifying them according to quartiles, in which the higher the incidence, the darker the color. The state of Pernambuco was visually divided into four MR: Metropolitan Region;*Agreste*;*Sertão*; and *Vale do São Francisco* and *Araripina*.

The spatial autocorrelation measure used was the global Moran's Index, which tests whether the connected areas present greater similarity regarding the indicator studied than expected in a random pattern, ranging from -1 to +1. The degree of existing autocorrelation can be quantified, being positive for direct correlation, negative for inverse correlation.[12]

In addition to the global Moran's Index, the local index was used, which resulted in a "Moran's map" of the average TB incidence rate, since it allows finding the "pockets" of spatial dependence not observed in the global indices, such as possible clusters and outliers. The relationships between the value of the measured attribute and its neighbors can be observed in the local indexgraphical analysis, called the Moran scatter diagram, or in the two-dimensional thematic map, called the Box Map.[12]

The graph is divided into quadrants: Q1, Q2, Q3 and Q4. The points located in Q1 and Q2 indicate areas in which the measured value of the attribute resembles the average of its neighbors. The first indicates a positive value and a positive average, and the second, a negative value and a negative average. The points located in Q3 and Q4 indicate that the value of the measured attribute does not resemble the average of its neighbors. In this case, Q3 indicates a negative value and a positive average, and Q4 indicates a positive value and a negative average. The areas located in Q3 and Q4 can be seen as extremes, or as transition areas, since they do not follow the pattern observed for their neighbors.[13]

Since this was a study that used official secondary data from the public domain, without identifying subjects, there was no need for assessment by a Research Ethics Committee (REC). The study followed the Brazilian National Health Council (In Portuguese, *Conselho Nacional de Saúde* - CNS) recommendations in its CNS Resolution 466 of December 12, 2012.

RESULTS

There were 56,711 confirmed cases of TB recorded per municipality of residence in Pernambuco during the study period. The overall average detection rate during the period was 35.6/100,000 inhabitants, with large disparities between the MR: the highest rate was recorded in MR 1, with 58.45 cases/100,000 inhabitants, and the lowest in MR 3, with 19.74 cases/100,000 inhabitants.

From 2011 to 2015, the detection rate for TB in Pernambuco was 34.1/100,000 inhabitants, with the highest rate being recorded in MR 1, with 55.99/100,000 inhabitants, and the lowest in MR 4, with 20.47/100,000 inhabitants. In the following period, Pernambuco recorded 37.32 cases/100,000 inhabitants, with MR 1 continuing to present the highest value (61.27 cases/100,000 inhabitants) compared to 18.89 cases/100,000 inhabitants in MR 3.

Below are indicators that may influence the persistence of TB as a public health concern. It can be seen that, although there is a mathematical similarity between the Gini Index, the urbanization rate and the HDI-income among the MR, the population density and the number of establishments in MR 1 are higher when compared to the other MRs (Table 1).

Table 1. Distribution of population density, Gini Index, urbanization rate, HDI-R* and commercial facilities rate for each health macroregion. Pernambuco, 2022.

Variables	Macro 1	Macro 2	Macro 3	Macro 2
Population density	516.8	120.46	40.9	27.25
GiniIndex	0.517	0.514	0.529	0.522
Urbanization rate	62.18	62.95	61.86	59.62
HDI-I	0.569	0.579	0.579	0.57
Trade	908.5	295.5	365.8	264.8

**HDI-I: Human Development Index – income*

TB detection rates for MR1 were higher in all periods compared to the other MR (Table 2).

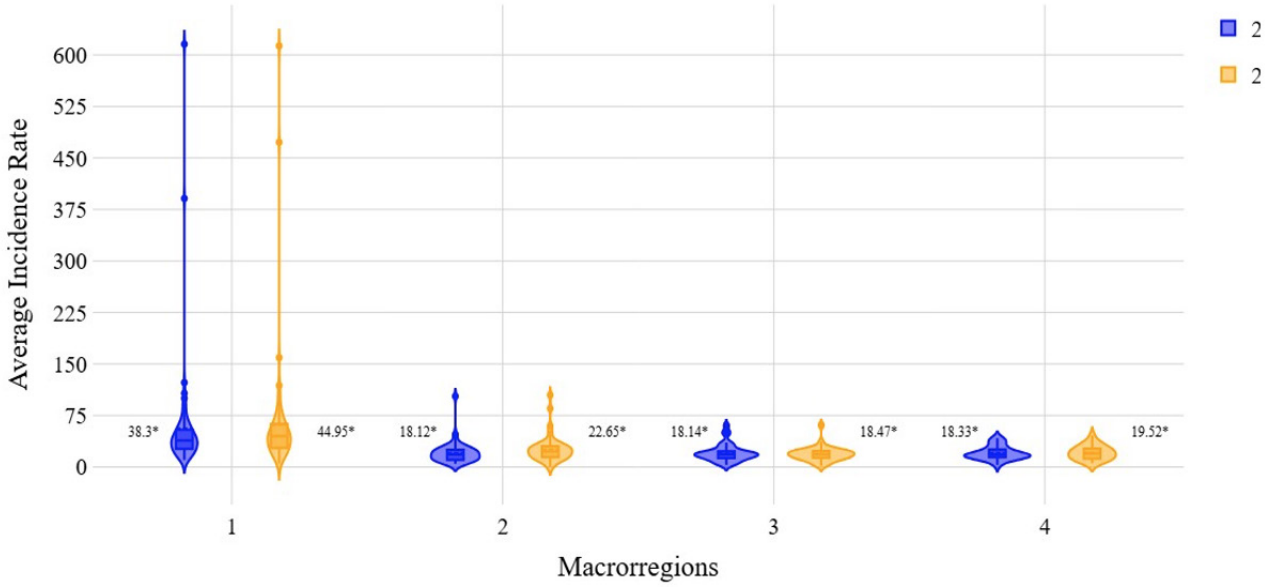
The highest ranges in TB detection rates are found in MR 1 (10.44–615.96 per 100,000 inhabitants), and the lowest in MR 3 (1.70–60.00 per 100,000 inhabitants). In the first five-year period, 50% of municipalities in MR 1 had up to 38.3 cases/100,000 inhabitants, rising to 44.95 in the second. This increase between periods was accompanied by all other MR. It is also observed that the median in MR 1 is higher than that of the others, showing that the problem is more present in this than in the other MR (Figure 2).

The comparison of the spatial distribution of the gross coefficient of the TB incidence rate in Pernambuco between the periods 2011-2015 (3A), 2016-2020 (3B) and 2011-2020 (3C). For all periods, the highest incidence rates were observed in MR 1 (above 37/100 thousand inhabitants) (Figure 3).

The letters D, E and F represent the Moran map of the TB incidence rate. One can see the existence of high-high clusters in the MRR and surrounding areas. Low-low clusters tend to be concentrated in the *Sertão* region of Pernambuco, which is home to MR 3 and 4 (Figure 3).

Table 2. Tuberculosis detection rates by macroregion per 100,000 inhabitants. Pernambuco, 2011-2015 and 2016-2020.

Period	Values	MR1	MR2	MR3	MR4
2011-2015	Minimum	10.44	4.63	2.91	2.87
	Average	55.99	20.41	20.73	20.47
	Maximum	615.96	103.22	60.57	42.06
2016-2020	Minimum	5.22	0.00	1.70	5.56
	Average	61.27	25.64	18.89	20.80
	Maximum	613.1	104.69	60.94	45.87
2011-2020	Minimum	9.55	4.24	8.77	4.22
	Average	58.45	22.99	19.74	20.52
	Maximum	608.63	104.03	56.12	43.86



Legend: A. Comparison of detection rate by macroregion in the period; B. Comparison of detection rate by macroregion considering the five-year periods.

Figure 2. Violin plots of median tuberculosis detection rates. Pernambuco, Brazil, 2022.

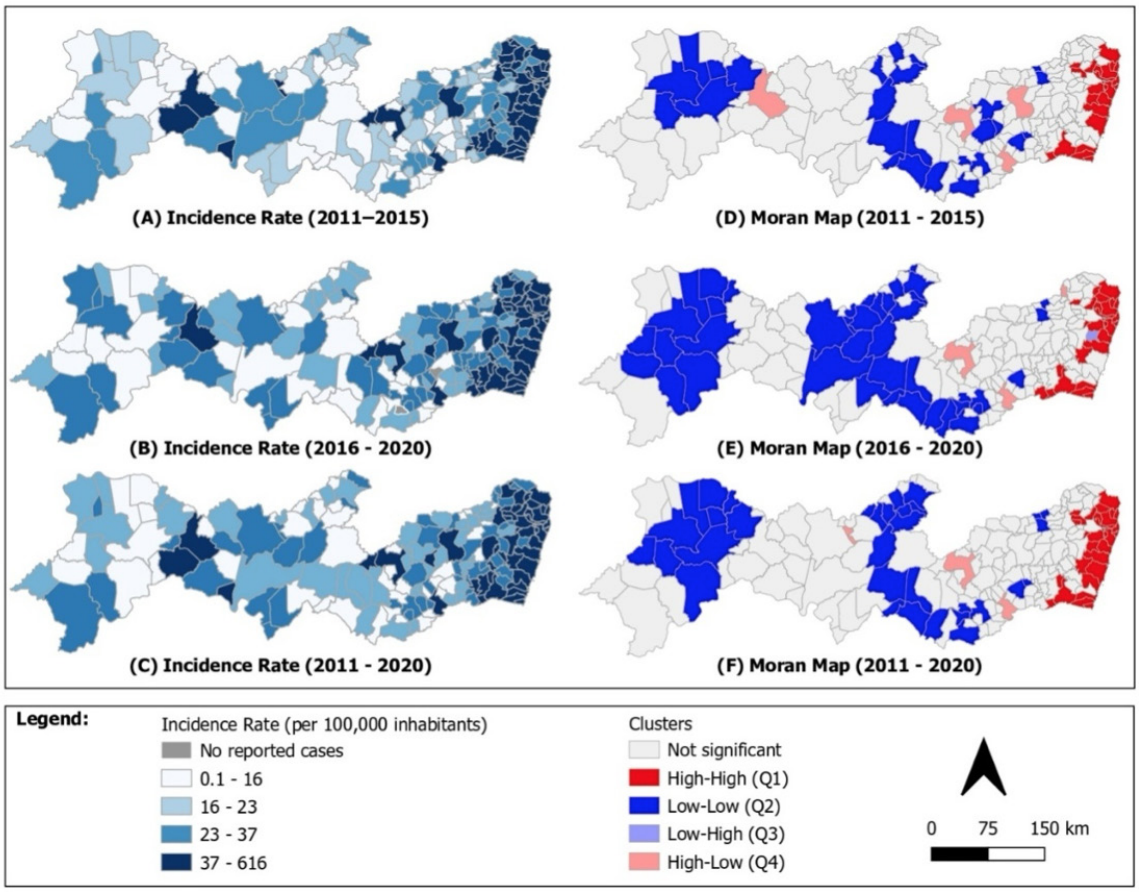


Figure 3. Spatial and temporal evolution of the gross incidence rate of tuberculosis (3A,B,C), and Moran map of the detection rate (3D, E, F).

DISCUSSION

There was an increase in the TB detection rate in Pernambuco between the five-year periods, with large disparities in values between the regions located in the countryside of the state (*Sertão*, *São Francisco* and *Araripe*) and the Metropolitan Region, with the highest values observed in the latter for the entire period, in addition to having the highest population density and the highest concentration of commercial establishments. The average detection rate for Pernambuco during the study period was higher than that for Brazil for the same period. Spatial analysis showed the existence of high--high clusters, with municipalities with high detection rates surrounded by others also with high rates in the MRR and surrounding areas.

This geographic disparity points to the relationship between clusters of TB cases and areas of high population density, which, in the case of Brazil, is compounded by specific issues. Metropolitan Regions, although notably responsible for part of the country's economic growth, due to the disorderly process of urbanization, have a chronic lack of urban infrastructure that has historically led people to seek housing in illegal subdivisions, a phenomenon known as peripheralization. These areas are characterized by great distance between social strata, high poverty, low levels of education, and difficulty in accessing essential services, among others.[13,14] The Social Vulnerability Atlas shows that the Gini coefficient is 0.616, in all Brazilian metropolises, and 0.593, in the rest of the country.[15]

The implementation and dissemination of specific control measures, such as improving patient search strategies, access to diagnosis and treatment within the care network structure adopted in Brazil, resulted, in the last ten years, in a 20.2% reduction in the incidence rates of the disease in Brazilian territory, which caused the rate to fall from 38.7 cases/100,000 inhabitants, in 2006, to 30.9 cases/100,000 inhabitants, in 2015, and from there to 35.28 cases per 100,000 inhabitants, in 2021.[16]

Continuing global efforts to control TB, the Sustainable Development Goals (SDGs) agenda succeeds that of the Millennium Development Goals (MDGs) and is more comprehensive and less individualistic, placing care for TB and other diseases within the objective of ensuring universal health coverage by strengthening the Primary Health Care network. Brazil's achievement in the MDGs served as a basis for adherence to the global target of reducing deaths by 95% and the incidence rate of the disease by 90% by 2035.[17]

Even with the reduction in TB cases in Brazil, Pernambuco is still the only northeastern state with a TB detection rate above 34 cases/100,000 inhabitants, exceeding the national average. Along with other Brazilian states located mainly in the North region, it continues to

negatively contribute to the failure to achieve global TB control goals.[16]

It can be seen that Pernambuco is moving in the opposite direction to other states in the northeast. Although far from achieving the SDGs, in Ceará, for a similar period, a decrease in incidence rates was observed, even though the problematic issue of the concentration of the highest rates in the MR remains.[18] In Paraíba, spatially similar findings were observed for the same period in the population under 15 years of age.[19] For the North region, a study carried out in Belém (PA) showed an incidence of 97.5/100 thousand inhabitants, well above the national average.[20]

Within this scenario, the significant increase in the TB detection rate between the two five-year periods may be related, in part, to the economic crisis of 2015, which occurred in Brazil, in which the Gross Domestic Product (GDP) fell by 3.62%, suffering the worst result in 25 years. This drop in GDP directly impacts Brazilian families, with a drop in purchasing power and other social factors, generating an increase in health needs and demand for public services, while the expansion of countries' health policies follows economic growth and declines in times of crisis and recession.[21] This vicious cycle may have impacted TB numbers in Pernambuco.

Bringing health data to this situation, a study is cited that found that the implementation of regionalized health surveillance in Pernambuco was incomplete for the first MR.[22] This fact implies the harm to the planning and promotion of strategies appropriate to the different realities of the municipalities, as would be the case of TB in Pernambuco.

The fact that TB is a multifactorial disease, with a biological cause, but whose expression in populations goes beyond individual determinants (smoking, alcoholism, etc.), clinical and socioeconomic factors (HIV co-infection, poverty, malnutrition, etc.), also partly explains the situation of the disease in Pernambuco. In this case, it is worth noting that the state is one of the most unequal in the country, and that the capital, Recife, was recently classified as the one where the poor are the poorest, which is reflected in neighboring municipalities.[18,19] Additionally, there is the fact that the Metropolitan Regions where the highest income ratios were recorded between the poorest and the richest, in ascending order, were Recife (21.0), Salvador (21.3), João Pessoa (21.6), Natal (23.9) and Aracaju (24.4).[23]

Hence, addressing the characteristics of Brazilian metropolitan regions, especially in the northeast, is imperative. Since its inception, the MRR has remained marked by social inequities. The process of economic dynamism with road improvements and industrialization that began in the 1980s and 1990s was not accompanied by positive social changes. Thus, Recife and its surrounding areas, despite economic improvements, have stabilized within the condition of an incomplete, peripheral and unequal regional metropolis.[24]

This issue deserves to be addressed globally. According to a 2019 United Nations report, around 1% of the richest Brazilians hold a third of the country's income, resulting in the second highest concentration of income in the world. Brazil's historical trajectory is biased towards protecting people at the top of the economic pyramid and making the lower-income population extremely vulnerable. In short, this situation acts as a filter, preventing any economic growth from being converted into social benefits. Applying these facts to TB, since it is a disease with a social background, it can be concluded that, if government action is not targeted at the most global determinants, TB control will always be far from happening.[25]

Spatial analysis reinforces what has already been explained, showing that TB tends to persist in areas where population growth is not accompanied by urban development, as occurs in most metropolitan regions in northeastern Brazil that suffer chronically from social vulnerability. The municipalities in Pernambuco that presented the lowest TB detection rates were Santa Filomena (Macro 4), Ibirajuba (Macro 2) and Terezinha (Macro 3).These last two did not show any cases of TB in the second five-year period (2016-2020). All three municipalities with the lowest rates are located in the countryside of the state, which may demonstrate a relationship of locomotion, employment opportunities and study in the capital, thus resulting in lower transmissibility compared to MR 1, which encompasses the highest rates of detection of the disease.

The fact that TB is a multifactorial disease, with a biological cause, but whose expression in populations goes beyond individual determinants (smoking, alcoholism, etc.), clinical and socioeconomic factors (HIV co-infection, poverty, malnutrition, etc.), also partly explains the situation of the disease in Pernambuco. In this case, it is worth noting that the state is one of the most unequal in the country, and that the capital, Recife, was recently classified as the one where the poor are the poorest, which is reflected in neighboring municipalities.[18,19]

As a limitation of this study, the use of secondary data, although useful, provides information of a general nature that, due to underreporting, may result in incompleteness of publicly available data. To mitigate the limitations, cross-validation strategies were adopted, comparing information from different sources to correct discrepancies. In addition, the application of statistical methods allowed us to correct gaps in the data, reinforcing the validity and reliability of results.

It is considered that this study was carried out before the pandemic period, when it would have been necessary to address other determining factors in the TB situation. In this case, the term "syndemic" should be cited as a process of synergistic interaction between two or more diseases, in which the effects are mutually potentiated. In the case of TB, during the pandemic period, globally and nationally, it was observed that the number of people with undiagnosed and untreated TB increased, resulting first in a greater number of deaths from TB and more community transmission of the infection and then, with some delay, a greater number of people developing TB.[8] The importance of this study is highlighted in the sense that it was carried out without the bias of the pandemic, in which there was a great reduction in both the general

economic gain and the supply of health services, which could be compromising.

Considering the concept of One Health, TB control requires contextual actions to improve people's general living conditions. In an unequal state like Pernambuco, this goal is difficult to achieve. Social support, which is so necessary in this situation, exists in Brazil, but it is intended for people in social vulnerability in general, with no specific support for people living with TB.

It is concluded that TB remains a serious public health problem in Pernambuco, especially in the MRR. The findings of this study help to perpetuate an image of TB as being linked to neglected and stigmatized segments that lack effective actions to eliminate the disease. Space-related information can support targeted and evidence-based decisions, such as monitoring data quality to improve the information system or establishing integrative social protection policies for key populations. Macroeconomic policies, mainly considering better income distribution, should be the government's target.

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AUTHORS' CONTRIBUTIONS

Gisele Matias de Freitas contributed to bibliographic research, abstract writing, introduction, methodology, discussion, interpretation and description of results, preparation of tables, conclusions, review and statistics. **Louisiana Regadas de Macedo Quinino** contributed to project management, bibliographic research, introduction, methodology, discussion, interpretation and description of results, and review. **Helena Manhães de Vasconcellos-** contributed to methodology, interpretation of results, preparation of tables, review and statistics. **Isabel Soares Diniz Oliveira** contributed to methodology, interpretation of results, preparation of tables, review and statistics.

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

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Corresponding Author:
Vinícius Vital de Oliveira
vinicius.oliveira@famed.ufal.br

Address: Avenida Dom Antônio Brandão, 239, Farol, 403-B, Maceió, Alagoas, Brazil.

Vinícius Vital de Oliveira[1];
Stephany Abdias Varjão[1];
Iramirton Figuerêdo Moreira[1];

[1] *Universidade Federal de Alagoas, School of Medicine, Campus A. C. Simões, Maceió, AL, Brazil.*

ABSTRACT

Background and Objectives: food allergy is a disease that has an abnormal immune response after contact with a certain food. It represents a significant disorder, as it involves dietary, social and psychological restrictions. Thus, this work aims to describe the profile of the people treated at an allergy and clinical immunology outpatient clinic of a university hospital in Maceió, Alagoas. **Methods:** this is a descriptive and quantitative study, based on the analysis of medical records of patients with food allergy treated at the *Hospital Universitário Professor Alberto Antunes* Allergy and Clinical Immunology Outpatient Clinic, from October 2016 to October 2023. **Results:** of the 678 patients, 233 were included, with a prevalence of women (61.8%) and an average age of 21.8 years (SD= ±17.1). The predominant allergens were seafood (25.9%), cow's milk protein (24.2%), egg (10.3%), fruits (9.3%), milk (7.6%), grains (5.8%), fish (4.1%), meat (4.1%), chocolate (2.0%) and vegetables (1.0%). **Conclusion:** the population studied in this research presents an epidemiological profile similar to the data in the literature, and shows characteristics that justify the need for greater attention to early diagnosis and treatment, since there was a prevalence of involvement in the age group of young adults who are economically active, in addition to the significant presence of common foods in the menu of the Brazilian population. Furthermore, the diagnosis of food allergy is shared with other immunoallergic diseases, which makes it essential to encourage studies that analyze the pathophysiological relationship between these.

Keywords**:** *Food Hypersensitivity. Epidemiology. Allergens. Allergy and Immunology.*

RESUMO

Justificativa e Objetivos: a alergia alimentar é uma doença que apresenta resposta imunológica anormal após contato com determinado alimento. Representa um transtorno significativo, pois envolve restrições alimentares, sociais e psicológicas. Assim, este trabalho tem como objetivo descrever o perfil epidemiológico das pessoas atendidas no ambulatório de alergia e imunologia clínica de um hospital universitário em Maceió, Alagoas. **Métodos:** trata-se

de estudo descritivo e quantitativo, a partir da análise de prontuários de pacientes com alergia alimentar atendidos no Ambulatório de Alergia e Imunologia Clínica do Hospital Universitário Professor Alberto Antunes, no período de outubro de 2016 a outubro de 2023. **Resultados:** dos 678 pacientes, 233 foram incluídos, com prevalência de mulheres (61,8%) e idade média de 21,8 anos. Os alérgenos predominantes foram frutos do mar (25,9%), proteína do leite de vaca (24,2%), ovo (10,3%), frutas (9,3%), leite (7,6%), grãos (5,8%), peixes (4,1%), carnes (4,1%), chocolate (2,0%) e vegetais (1,0%). **Conclusão:** a população estudada nesta pesquisa apresenta um perfil epidemiológico semelhante aos dados da literatura, e evidencia características que justificam a necessidade de maior atenção quanto ao diagnóstico e tratamento precoce, visto que houve uma prevalência do acometimento da faixa etária de adultos-jovens que são economicamente ativos, além da presença significativa de alimentos comuns no cardápio da população brasileira. Ademais, o diagnóstico da alergia alimentar é compartilhado com outras doenças imunoalérgicas, o que torna essencial o incentivo de estudos que analisem a relação fisiopatológica entre essas.

Descritores: *Hipersensibilidade Alimentar. Epidemiologia. Alérgenos. Alergia e Imunologia.*

RESUMEN

Justificación y Objetivos: la alergia alimentaria es una enfermedad que presenta una respuesta inmunológica anormal tras el contacto con un determinado alimento. Representa un trastorno importante, ya que implica restricciones dietéticas, sociales y psicológicas. Por lo tanto, este trabajo tiene como objetivo describir el perfil de las personas atendidas en un ambulatorio de alergia e inmunología clínica de un hospital universitario de Maceió, Alagoas. **Métodos:** se trata de un estudio descriptivo y cuantitativo, basado en el análisis de historias clínicas de pacientes con alergia alimentaria atendidos en el Ambulatorio de Alergia e Inmunología Clínica del *Hospital Universitário Profesor Alberto Antunes*, de octubre de 2016 a octubre de 2023. **Resultados:** 678 pacientes, 233 Se incluyeron, con predominio de mujeres (61,8%) y edad media de 21,8 años. Los alérgenos predominantes fueron mariscos (25,9%), proteínas de la leche de vaca (24,2%), huevo (10,3%), frutas (9,3%), leche (7,6%), cereales (5,8%), pescado (4,1%), carne (4,1%), chocolate (2,0%) y hortalizas (1,0%). **Conclusión:** la población estudiada en esta investigación presenta un perfil epidemiológico similar a los datos de la literatura, y destaca características que justifican la necesidad de una mayor atención en cuanto al diagnóstico y tratamiento temprano, ya que prevaleció la afectación en el grupo etario de adultos jóvenes con recursos económicos. activo, además de la importante presencia de alimentos comunes en el menú de la población brasileña. Además, el diagnóstico de la alergia alimentaria es compartido con otras enfermedades inmunoalérgicas, lo que hace imprescindible impulsar estudios que analicen la relación fisiopatológica entre estas enfermedades.

Palabras Clave: *Hipersensibilidad Alimentaria. Epidemiología. Alérgenos. Alergia e Inmunología.*

INTRODUCTION

Food allergy (FA) is defined as a specific and adverse health response resulting from an abnormal immunological mechanism that occurs after contact with a certain food, and can be divided into three groups, according to the immunological process involved, namely: IgE-mediated; non-IgE-mediated; and mixed reactions.[1] Although data on the prevalence of food hypersensitivity reactions are conflicting, there has been an increase in cases in recent decades worldwide. The prevalence is estimated to be 6% to 8% in children up to 3 years of age, while in adults it ranges from 2% to 4%.[1,2] Family history, lifestyle changes and new eating habits in the population are very important in the increase in cases of FA.[1-3]

Furthermore, numerous foods have been recognized as allergens, but only a small portion of them have been responsible for the majority of reported reactions. This varies according to age group, geographic region of patients, and the large difference between the perception of symptoms related to a given food and the correct diagnosis of FA. Therefore, it is important to record the epidemiology of these events and their pattern of occurrence in the study population.[4]

It is also worth noting that FA represents a significant disorder imposed on the person who has it, as it often involves dietary and social restrictions, high levels of anxiety, as well as direct consequences of the immune system hyper-reactivity, such as severe reactions and potential subsequent fatalities.[4] In this regard, adequate management is essential in order to guarantee quality of life and well-being, capable of reducing negative outcomes, such as impacts on social life, work and personal limitations of individuals who are affected by this clinical condition.[5,6]

Understanding the prevalence profile of FA is therefore essential to ensure the best management of patients affected by this condition, considering the variables related to the presentation of each allergic condition. These variables, which involve everything from age to diverse exposure to allergens, are responsible for the uncertainties in global prevalence studies. Thus, as a potentially useful tool for planning objective actions aimed at improving and expanding care services, for earlier diagnosis and treatment, this study aimed to describe the profile of people treated at an allergy and clinical immunology outpatient clinic of a university hospital in Maceió, Alagoas.

METHODS

This is a descriptive study with a quantitative approach, based on documents, carried out through physical and electronic medical records of patients with FA treated at the *Hospital Universitário Professor Alberto Antunes* (HUPAA) Allergy and Clinical Immunology Outpatient Clinic in Maceió, Alagoas.

The HUPAA Allergy and Clinical Immunology Outpatient Clinic has been a state reference in the management of allergic patients since 1995. However, the provision of specialized services in this area began in 2016, which is why the period from this year until October 2023 was considered to select the medical records. This time interval was delimited to cover the longest possible period, including from the initial point of specialized care in allergy and clinical immunology at HUPAA until the deadline for collecting the analyzed data, from June to October 2023. During this period of specialized care, 678 medical records were recorded. Thus, the study includes all patients who were and still are treated by this reference service in the state's public health, who met the eligibility criteria.

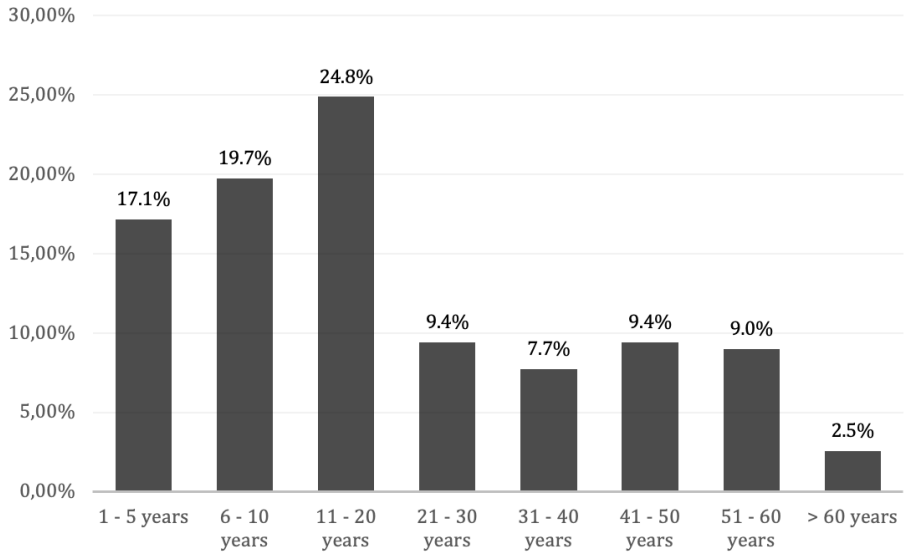
Inclusion criteria comprised medical records of patients diagnosed with FA, such as cow's milk protein allergy (CMPA), seafood (shrimp, fish and crustaceans), fruits (watermelon, pineapple, strawberry, coconut, cocoa), chocolate, grains (soy, corn, wheat, peanuts and nuts), meat, fish, eggs, milk and vegetables. For the diagnosis, the specific sensitization test and oral provocation test were considered. Thus, 233 medical records of patients with some type of FA were obtained, selected because they presented all the data necessary for epidemiological analysis. In turn, the exclusion criteria established included patients followed up in the outpatient clinic for other immunoallergic diseases exclusively and patients who only had a suspicion of FA. Moreover, medical records with incomplete data documentation were discarded, as they did not present sufficient information to conclude the study.

The epidemiological data collected from medical records were sex, age, foods recognized as allergenic substances and concomitant presence of FA and other immunoallergic diseases in this study population. After data collection, they were analyzed using descriptive statistics in Microsoft Office Word®, and, for better data visualization, tabular and graphical representation were used.

In compliance with Resolution 466/12 of the Brazilian National Health Council,[7] this project was approved by the Research Ethics Committee of HUPAA/UFAL/EBSERH, under Certificate of Presentation for Ethical Consideration (CAAE - *Certificado de Apresentação para Apreciação Ética*) 67320823.0.0000.0155 and Opinion 6.010.320, with approval date 05/18/23. The anonymity and confidentiality of the information obtained as well as all other prerogatives were guaranteed.

RESULTS

Of the 678 medical records registered at the HUPAA outpatient clinic, 233 patients were diagnosed with allergy to a specific food and met the inclusion criteria for the study. Therefore, 406 medical records were excluded from the total registered in the chosen period because they did not meet all the eligibility criteria. Of the 233 patients, the majority were female (61.8%), with a mean age of 21.8 years (SD=±17.1), with a minimum of 1 year and a maximum of 84 years, with emphasis on the youngest sample group (11 to 20 years – 24.8%) (Graph 1).



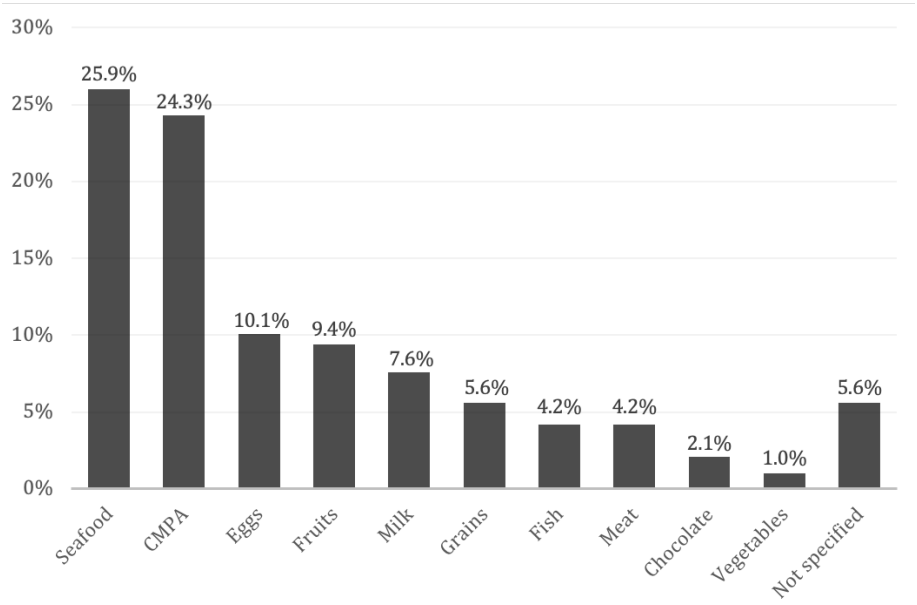
Source: Hospital Universitário Professor Alberto Antunes Allergy and Clinical Immunology Outpatient Clinic medical records (2016-2023).

Graphic 1. Age distribution of patients with food allergy treated at the Hospital Universitário Professor Alberto Antunes Allergy and Clinical Immunology Outpatient Clinic. Maceió, Alagoas, Brazil, 2016-2023.

Among the main allergens identified in the study, seafood (25.9%) stands out, especially shrimp (72.0%), CMPA (24.3%), egg (10.1%) and fruits (9.4%), with pineapple being responsible for the diagnosis of immunological sensitivity with the highest record within the sample (55.5%). Furthermore, CMPA (7.6%), grains (5.6%), such as wheat, peanuts, soy, corn and nuts, fish (4.2%), meat (4.2%), chocolate (2.1%) and vegetables (1.0%) were also identified. It is noteworthy that 5.5% of patients have FA to some allergen not specified in medical records. This occurs because diagnostic tests were inconclusive in identifying the specific allergen, however they presented clinically positive results, which is recorded as unspecified FA (Graph 2).

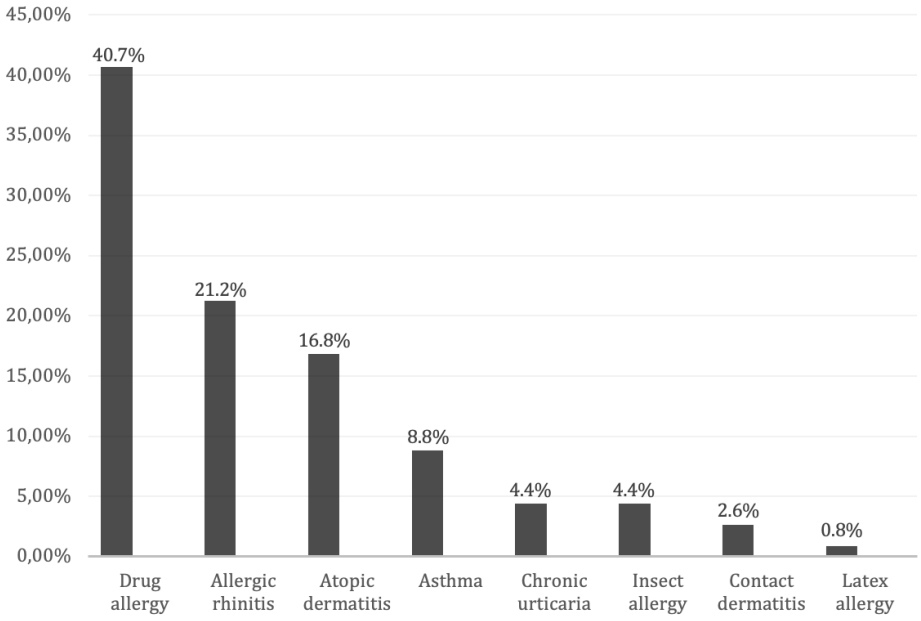
The distribution of food allergens by age group showed the prevalence of CMPA up to 20 years (95.7%), seafood, from 21 to 60 years (68%), eggs, between 1 and 20 years (72.4%), fruits, between 6 and 10 years (29.6%), milk, between 1 and 20 years (72.7%), and other foods, with equivalent distribution between age groups (Table 1).

It was also evident that 47.2% of patients concomitantly had other allergies or immunoallergic diseases, such as drug allergy (40.7%) and allergic rhinitis (21.2%) (Graph 3).



Source: Hospital Universitário Professor Alberto Antunes Allergy and Clinical Immunology Outpatient Clinic medical records (2016-2023).

Graphic 2. Distribution of allergens identified in patients with food allergy treated at the Hospital Universitário Professor Alberto Antunes Allergy and Clinical Immunology Outpatient Clinic. Maceió, Alagoas, Brazil, 2016-2023.



Source: Hospital Universitário Professor Alberto Antunes Allergy and Clinical Immunology Outpatient Clinic medical records (2016-2023).

Graphic 3. Distribution of other immunoallergic diseases in patients with food allergy treated at the Hospital Universitário Professor Alberto Antunes Allergy and Clinical Immunology Outpatient Clinic. Maceió, Alagoas, Brazil, 2016-2023.

Table 1. Distribution of food allergens according to age group of patients with food allergy treated at the Hospital Universitário Professor Alberto Antunes Allergy and Clinical Immunology Outpatient Clinic. Maceió, Alagoas, Brazil, 2016-2023.

Types of allergens	Age groups															
	1-5 years		6-10 years		11-20 years		21-30 years		31-40 years		41-50 years		51-60 years		<60 years	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Seafood	1	2%	8	13.7%	15	22.3%	12	46.1%	9	39.1%	14	48.2%	15	51.7%	1	14.2%
Cow's milk protein	33	66%	17	29.3%	17	25.3%	1	3.8%	1	4.3%	-	-	1	3.4%	-	-
Egg	6	12%	10	17.2%	5	7.4%	1	3.8%	4	17.3%	-	-	1	3.4%	2	28.5%
Fruits	3	6%	8	13.7%	3	4.4%	4	15.3%	1	4.3%	4	13.7%	2	6.8%	2	28.5%
Milk	3	6%	4	6.8%	9	13.4%	1	3.8%	1	4.3%	3	10.3%	1	3.4%	-	-
Grains	3	6%	3	5.1%	3	4.4%	1	3.8%	1	4.3%	1	3.4%	4	6.8%	1	14.2%
Fish	1	2%	2	3.4%	-	-	2	7.6%	3	13%	3	10.3%	1	3.4%	-	-
Meat	-	-	3	5.1%	4	5.9%	1	3.8%	1	4.3%	2	6.8%	1	3.4%	-	-
Chocolate	-	-	1	1.7%	3	4.4%	1	3.8%	-	-	-	-	1	3.4%	-	-
Vegetables	-	-	1	1.7%	-	-	-	-	-	-	1	3.4%	-	-	1	14.2%
Not specified	-	-	1	1.7%	8	11.9%	2	7.6%	2	8.6%	1	3.4%	2	6.8%	-	-

Source: Hospital Universitário Professor Alberto Antunes Allergy and Clinical Immunology Outpatient Clinic medical records (2016-2023).

DISCUSSION

According to the World Health Organization (WHO), 200 to 250 million people suffer from allergies to some type of food,[8] a scenario in which FA is currently a serious public health concern that has been growing throughout the world, especially in industrialized countries. The urban lifestyle favors the development of risk factors for the disease, such as easy exposure to allergens, misuse of antibiotics, changes in intestinal flora and microbial effects on the immune system.[9] Furthermore, these countries provide a more advanced research arsenal in identifying FA, which is not the reality in Brazil, given that there is no precise epidemiological data on the subject in the country.[9,10] Therefore, FA deserves special attention from healthcare services and public policies, as it is a clinical condition capable of affecting quality of life and generating serious complications in individuals affected by this disease.[10,11]

The majority of patients in this study were female. According to the literature, women tend to have more FA diagnoses than men, however there is little scientific evidence to justify this reason, since the numbers presented in the literature vary widely, such as 46.34% in the study by Andrade *et al.*[12] and 81.1% in the study by Costa *et al.*[13] Furthermore, Lobo[9] mentions male sex as a risk factor for the disease, which makes this relationship between sex and FA questionable, as it does not yet present a solid analysis.[9,12]

Regarding age group, the study showed a prevalence among young people in the first two decades of life (1-20 years), supporting the literature.[14,15] The higher prevalence in this age group is explained by the relationship with genetic predisposition, environmental factors and the influence of early exposure to allergens, contributing to the development of FA, especially in the first two years of life.[16] Then, as the immune system matures, these hypersensitivities are overcome during the transition to adulthood,[2] with only 10% of the group that already had this disease in early childhood persisting.[17]

Studies report that, among the most prevalent foods in the child population, cow's milk, eggs, soy and wheat are the most prominent allergens.[1] Thus, it is worth noting that the present study also highlighted these same foods as the main allergens and that CMPA in childhood deserves special attention, since, in this research, there was a prevalence of 24.3%. In national territory, there is a prevalence of 5.4% and an incidence of 2.2% of CMPA in children aged less than or equal to 24 months.[2,18,19]

Therefore, early diagnosis of this specific condition becomes essential, as it is a determining factor for therapeutic conduct, which is based on an exclusion diet and the use of infant formulas, affecting the immunological and emotional development of these children, in addition to impacting the mother-child relationship and financial aspects.[18,19] In the older age groups (21-50 years), the most prevalent allergy-causing foods in this study were seafood and fish, eggs, fruits and grains.[1,19] Similar results are found in the literature, where shellfish, dairy products, eggs and grains are among the most prevalent allergens in the study population.[20,21] This data is supported by scientific analyses that show that FA triggered by allergens such as peanuts, fish and seafood are considered persistent and, therefore, tend to remain from childhood to adulthood.[22] This occurs due to a failure in the allergen tolerability mechanism during the immune system maturation, since these foods have glycoproteins that are resistant to the digestion and cooking processes, favoring the phenomenon of cross-reactivity with other allergens that carry similar amino acids.[23,24]

The current exponential growth of adults and older adults, associated with environmental and lifestyle changes, has partially altered epidemiological data on FA, since the increasing incidence of this pathology even at advanced ages reveals the emergence of a new scenario for allergies, considering that the presence of FA among older adults is around 10%, with a tendency to increase

over the next few years.[25] However, underdiagnosis is still a reality for this age group, as the immunopathological mechanism related to the phenomenon of immunosenescence is not well understood, which also makes it difficult to recognize clinical manifestations, which may be present in small quantities, be confused with other age-related diseases, or even be masked by the use of medications.[1,17]

Another aspect of analysis is the presence of FA concomitant with other types of allergic diseases, with drug allergy, allergic rhinitis, atopic dermatitis (AD) and allergic asthma being the most frequent in both this study and in the literature.[26] Concerning drug allergy, there is still a lack of studies that demonstrate a direct association with FA. However, allergic rhinitis, AD and asthma are considered diseases of the atopic march, and there is an important predisposition relationship between these diseases and the development of FA, especially in children.[25] This relationship is due to the strongest known risk factor for FA, which is eczema, a classic clinical manifestation of AD, since the damaged skin barrier can allow the absorption of food allergens through the skin, triggering, in turn, an immunological response of food sensitization and allergy in the absence of pre-existing oral tolerance to these foods. However, this mechanism still remains inconclusive, being influenced by genetic and environmental theories.[16] Furthermore, cohort studies on the atopic march have shown that 40% of children with AD have FA, with the severity of this dermatological pathology being an aggravating factor for the development of food hypersensitivity. [27,28]

Therefore, the epidemiological study of patients with FA registered at the HUPAA Allergy and Clinical Immunology Outpatient Clinic is similar to that described in the world literature and serves as an epidemiological basis in the Brazilian population and in the Northeast region for new studies and future interventions in the area. There was a predominance of the disease in the pediatric group than in the adult group as well as the most frequent allergens, such as CMPA, cow's milk, eggs and seafood. Furthermore, the concomitant presentation of other allergies with FA, such as drug allergy, allergic rhinitis and allergic asthma, stood out, a situation that worsens the quality of life of patients with FA.

Thus, it is important to recognize FA in healthcare services, with the purpose of adopting measures in the planning of actions aimed at the diagnosis and treatment of these patients, which ratifies the need to value reference centers for allergic diseases in the Brazilian Health System to approach these patients and, with this, modify the growing scenario of this disease and its impacts on health and the economy.

It is also worth noting that the lack of a broad research arsenal in the area and the difficulty in accessing physical medical records were barriers that delayed the development of the study, making it necessary to expand the search for data and analysis time. Thus, it is essential to develop future studies on this topic so that the epidemiological understanding of FA acquires an increasingly broad analysis in the national scenario and that health promotion policies can be created in order to improve the quality of care for its carriers.

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AUTHORS' CONTRIBUTIONS

Vinícius Vital de Oliveira contributed to bibliographic research, abstract writing, introduction, methodology, discussion, interpretation and description of results, preparation of tables, conclusions, review and statistics. **Stephany Abdias Varjão** contributed to bibliographic research, abstract writing, introduction, methodology, discussion, interpretation and description of results, preparation of tables, conclusions, review and statistics. **Iramirton Figuêredo Moreira** contributed to project management, abstract writing, methodology, interpretation of results, conclusions and review.

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

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ORIGINAL ARTICLE

Clinical, epidemiological, and laboratorial profile of arboviruses of suspected cases during Brazilian Zika virus emergence

Perfil clínico, epidemiológico y de laboratorio de casos sospechosos de arbovirus durante la emergencia del virus Zika en Brasil

Perfil clínico, epidemiológico e laboratorial de casos suspeitos de arboviroses durante a emergência do Zika vírus no Brasil

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Corresponding Author:
José Henrique Francisco Roma
j262321@dac.unicamp.br

Universidade Federal de Rondonópolis, Faculdade de Ciências da Saúde. Avenida dos Estudantes 5.055, Cidade Universitária, Rondonópolis, MT 78735-910, Brasil.

José Henrique Francisco Roma[1];
Rachel Cruz Alves[2];
Ludiele Souza Castro[3];
Márcio José Ferreira[3];
Claudinéia de Araújo[3];
Bruno Moreira Carneiro[3];
Renata Dezengrini Slhessarenko[2];
Juliana Helena Chavez Pavoni[3];
Mariângela Ribeiro Resende[1];

[1] *Universidade Estadual de Campinas, Campinas, SP, Brasil.*
[2] *Universidade Federal de Mato Grosso, Cuiabá, MT, Brasil.*
[3] *Universidade Federal de Rondonópolis, Rondonópolis, MT, Brasil.*

ABSTRACT

Background and Objectives: Arboviruses are public health issues worldwide related to severe human health impairment. These viruses cause similar acute febrile syndromes, challenging differential diagnosis and adequate notification. The work aimed to describe the epidemiological and laboratorial profile of arboviruses of suspected cases reported in southeastern Mato Grosso (MT) during the Zika virus emergence in Brazil. **Methods:** Epidemiological and clinical features of arboviruses were analyzed in a descriptive and retrospective study. Serum samples were assessed by real-time reverse transcriptase polymerase chain reaction for detection of Zika, Dengue and Chikungunya, and by immunoassay for detection of IgM and IgG against Zika. **Results:** Of 197 patients, 63% were female, eight were pregnant. Mean age was 32 years old, with 44% between 19-59 years old; 28% were white, 34% had educational instruction, and 58.9% were urban residents. About 61% of cases occurred during rainy seasons, with 12.1% in three regions of the study area. Musculoskeletal disorders were the main complaints (22.8%), followed by fever (13.7%), rash and petechiae (12.6%), headache (11.7%), itching (10%), ophthalmological manifestations (6.1%) and gastrointestinal manifestations (5.6%). By means of molecular assays, 8.9% and 1.7% of Zika and Dengue were detected, respectively, in the samples tested. Serological assays for Zika showed 10.6% of positive samples for IgM and 55.8% for IgG. **Conclusions:** This study provides clinical, epidemiological, and laboratorial profile of Zika virus emergence in high-endemicity setting of dengue. The study relevance is understanding the introduction and concomitant occurrence of a new arbovirus disease.

Keywords: *Arboviruses. Epidemiology. Molecular Diagnostic. Serology.*

RESUMEN

Justificación y Objetivos: Los arbovirus son problemas de salud pública en todo el mundo relacionados con graves daños a la salud humana. Estos virus causan síndromes febriles agudos similares, lo que dificulta el diagnóstico diferencial y la notificación adecuada. El trabajo tuvo como objetivo describir el perfil epidemiológico y de laboratorio de los casos sospechosos de arbovirus notificados en el sudeste de Mato Grosso (MT) durante la emergencia del virus Zika en Brasil. **Métodos:** Se analizaron las características epidemiológicas y clínicas de los arbovirus en un estudo descriptivo y retrospectivo. Las muestras de suero se evaluaron mediante reacción en cadena de la polimerasa cuantitativa en tiempo real con transcripción inversa para la detección de de Zika, Dengue y Chikungunya. Anticuerpos IgM y IgG anti-Zika fueron detectados mediante inmunoensayo. **Resultados:** De 197 pacientes, 63% eran mujeres y ocho estaban embarazadas. La edad media fue de 32 años, con 44% entre 19-59 años; 28% eran blancos; 34% tenían instrucción educativa; y 58,9% eran residentes urbanos. Alrededor del 61% de los casos ocurrieron durante las temporadas de lluvias, con 12,1% en tres regiones del área de estudio. Los trastornos musculoesqueléticos fueron las principales quejas (22,8%), seguidos de fiebre (13,7%), erupción y petequias (12,6%), dolor de cabeza (11,7%), picazón (10%), manifestaciones oftalmológicas (6,1%) y gastrointestinales (5,6%). Mediante pruebas moleculares se detectó un 8,9% y un 1,7% de Zika y Dengue, respectivamente, en las muestras analizadas. Las pruebas serológicas para Zika arrojaron un 10,6% de muestras positivas para IgM y un 55,8% para IgG. **Conclusiones:** Este estudio proporciona un perfil clínico, epidemiológico y de laboratorio de la aparición del virus Zika en uma región de alta endemicidad del dengue. La relevancia del estudio es comprender la introducción y aparición concomitante de una nueva enfermedad por arbovirus.

Palabras Clave: *Arbovirus. Epidemiología. Diagnóstico Molecular. Serología.*

RESUMO

Justificativa e Objetivos: Arboviroses impactam a saúde pública mundialmente, causando graves prejuízos à saúde humana. Os arbovírus causam síndromes febris agudas semelhantes, desafiando o diagnóstico diferencial e a notificação adequada. O objetivo desta pesquisa foi descrever o perfil epidemiológico e laboratorial dos casos suspeitos de arboviroses notificados no sudeste de Mato Grosso (MT) durante a primeira emergência brasileira do Zika vírus. **Métodos:** as características clínicas e epidemiológicas das arboviroses foram analisadas de forma retrospectiva e descritiva. Amostras de soro foram avaliadas por reação em cadeia da polimerase em tempo real via transcriptase reversa para detecção de Zika, Dengue e Chikungunya, e por imunoensaio para detecção de IgM e IgG contra Zika. **Resultados:** Dos 197 pacientes, 63% eram do sexo feminino e oito estavam grávidas. A média de idade foi de 32 anos, dos quais 44% tinham entre 19 e 59 anos; 28% eram brancos; 34% eram alfabetizados; e 58,9% eram residentes urbanos. Cerca de 61% dos casos ocorreram durante os períodos chuvosos, sendo 12,1% em três regiões da área de estudo. Os distúrbios musculoesqueléticos foram as principais queixas (22,8%), seguidos de febre (13,7%), exantema e petéquias (12,6%), cefaleia (11,7%), prurido (10%), manifestações oftalmológicas (6,1%) e manifestações gastrointestinais (5,6%). Por meio de ensaios moleculares, foram detectados 8,9% e 1,7% de Zika e Dengue, respectivamente, nas amostras testadas. Os ensaios sorológicos para Zika mostraram 10,6% de amostras positivas para IgM e 55,8% para IgG. **Conclusão:** Este estudo fornece o perfil clínico, epidemiológico e laboratorial da emergência do Zika vírus em ambientes de alta endemicidade de dengue. A relevância do estudo é compreender a introdução e ocorrência concomitante de uma nova arbovirose.

Descritores: *Arboviroses. Epidemiologia. Diagnóstico Molecular. Sorologia.*

INTRODUCTION

Several required conditions are associated with the emergence of a new arboviral disease. Both introduction and dissemination must occur simultaneously to support the maintenance of complex cycles involving vectors, hosts, and human infection. In Brazil, the current climate changes associated with deforestation and socioeconomic conditions of the population represent critical aspects that are favorable to the emergence and reemergence of arboviruses transmitted by *Aedes* (*Stegomyia*) *aegypti* and *Aedes* (*Stegomyia*) *albopictus* mosquitoes.[1]

Although a significant number of Zika (ZIKV), Dengue (DENV), and Chikungunya (CHIKV) infections is asymptomatic, these viruses are responsible for moderate and severe syndromes. The acute febrile syndrome caused by DENV has been a significant public health challenge worldwide for decades, with a dramatic increase in cases in recent years, and it has been responsible for about 5,486 deaths until 39th epidemiological week of 2024 in Brazil.[2] Additionally, in recent years, two new emerging arboviruses were introduced in Brazil, ZIKV and CHIKV, both of which cause acute febrile syndromes and a severe impairment for human health. CHIKV is responsible for severe cases of polyarthralgia, and ZIKV, for congenital zika syndrome (CZS), leading to neuronal abnormalities, delayed neuro-psychomotor development in newborns, and Guillain-Barré syndrome (GBS) in adults, representing a public health emergency of international concern according to the World Health Organization.[3-4]

The clinical symptoms associated with these arbo-

viral infections are quite similar, especially in mild cases. Gastrointestinal, musculoskeletal, hematological, ophthalmological disorders, fever, itching, and headache are nonspecific symptoms of arboviral diseases, which hinder the differential clinical diagnosis and the correct notification of suspected cases. Therefore, effective notification associated with accurate diagnosis and the correct use of the Brazilian Health Information System are paramount and represent an impacting factor for public health.[5] The work aimed to describe the epidemiological and laboratorial profile of arboviruses of suspected cases reported in southeastern Mato Grosso (MT) during the emergence of ZIKV in Brazil.

METHODS

Study population

A retrospective and experimental study of suspected cases of arboviruses DENV, ZIKV and CHIKV fever reported in the municipality of Rondonópolis from August 2015 to August 2016 was carried out. During this period, Brazil experienced the emergence and dissemination of ZIKV.

Suspected cases of arboviruses assisted by the municipality's Primary Care Health Units were referred to the Central Laboratory of Rondonópolis, and clinical serum samples were obtained. The collected samples underwent molecular and serological analysis at the *Universidade Federal de Rondonópolis* Laboratory of Basic and Applied Virology. The study included patients up to five days after the onset of symptoms during the introduction of ZIKV in Brazil (2015-2016). Samples with more than five days of the onset of symptoms, insufficient volume for laboratorial analysis and inadequate storage conditions were excluded. Epidemiological data were obtained from July 2019 to November 2019 by notifiable forms, according to the Notifiable Diseases Information System (In Portuguese, *Sistema de Informação de Agravos de Notificação* - SINAN) of the Ministry of Health Brazil.

Demographic and clinical information analysis

The descriptive study was performed using sociodemographic and epidemiological data from 197 SINAN notifications; of these, 179 samples were included in laboratory analysis. Data were tabulated and analyzed using Microsoft Excel® (Washington, USA). The spatial distribution of patients' household was achieved from the open-source Geographic Information System (QGIS v3.18) software.

Laboratory analysis

Molecular investigation was performed by reverse transcription quantitative real-time polymerase chain reaction (RT-qPCR) in serum samples. The RNA was extracted and purified from 150µL of serum using silica columns (NucleoSpin® RNA Virus, Macherrey-Nagel, GER) according to the manufacturer's instructions. The one-step real-time ZDC Multiplex RT-PCR Assay® (BioRad, USA) was performed for RNA detection of DENV, ZIKV, and CHIKV viruses, following the manufacturer's instructions, on a CFX96 Touch™ Thermal Cycler (BioRad, USA).

Serological assessment was performed by enzyme-linked immunosorbent assay (ELISA) to detect immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies anti-ZIKV according to the manufacturer's instructions (Euroimmun AG, GER).

The interpretation of serological results was conducted carefully, considering the possibility of cross-reaction among arboviruses. In this regard, the molecular and serological diagnosis employed in this study present specific features, as shown on Table 1.[6]

The study was conducted obeying the ethical aspects that regulate scientific research involving human, according to Resolution 466/12 of the Brazilian National Health Council, and was approved by the *Universidade Federal de Mato Grosso* Research Ethics Committee, under CAAE 10767319.8.0000.8088.

RESULTS

This study included 197 patients with acute febrile syndrome and clinical suspicion of DENV, ZIKV, or CHIKV infections. According to the 197 patients' SINAN forms, 124 (63%) were female; of these, eight were pregnant, four in the first trimester and the other half in the third trimester of pregnancy. The mean age was 32 years old, and the youngest patient was two months old, whereas the oldest was 70 years old. The most frequent age group was 19-59 years old. Considering ethnic identity, 28% of

Table 1. Comparative analysis of molecular and serological methods for arbovirus diagnosis.

	Diagnostic assay	
	Molecular	**Serology**
Sampling	Acute phase - until 5th day of symptoms	Late phase - after 6th day of symptoms
Sample	Serum	Serum
Storage	-80°C	-20°C
Detection	Antigen - Viral RNA	Antibodies - IgM/IgG
Advantages	Early diagnosis	Lower cost
	High specificity and sensitivity	Easy technique execution
	Accurate and differential diagnosis	Tool for epidemiological surveillance
	Tool for molecular epidemiological surveillance - genome sequencing	Assessment and monitoring of the immune response
Disadvantages	Higher cost	Low specificity
	Complex technique execution	Cross-reaction with other arboviruses
		Inconclusive diagnosis

Legend: RNA – ribonucleic acid; IgM – immunoglobulin M; IgG – immunoglobulin G.

Table 2. Sociodemographic features of arboviruses of suspected cases in Rondonópolis, Brazil, during the ZIKV Brazilian epidemic (2015–2016).

	Frequency	
Variables	**n (197)**	**%**
Gender		
Female	124	63.0
Male	69	35.0
Ignored	4	2.0
Age range (years)		
0–5	16	8.1
5–19	14	7.1
19–59	88	44.7
59–70	10	5.1
Ignored	69	35.0
Ethnicity/skin color		
White	56	28.4
Black	7	3.6
Yellow	0	0
Brown	38	19.3
Indigenous	3	1.5
Ignored	93	47.2
Educational level		
Unlettered	1	0.5
Incomplete ES	19	9.7
Complete ES	4	2.0
Incomplete HS	6	3.0
Complete HS	14	7.1
Incomplete UE	5	2.5
Complete UE	19	9.7
Unapplicable	17	8.6
Ignored	112	56.9
Area of residence		
Urban	116	58.9
Countryside	4	2.0
Peri-urban	1	0.5
Ignored	76	38.6

Legend: ES: elementary school; HS: high school; UE: university education.

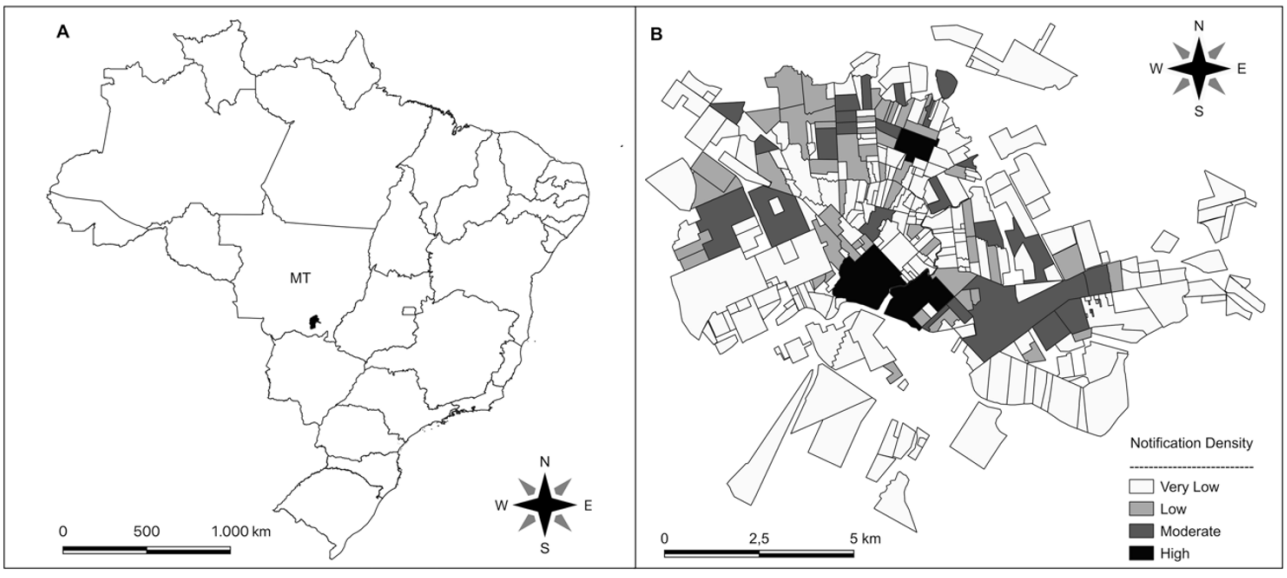
patients self-declared as white, and three cases were reported as indigenous. The educational level was missing in 57% of notification forms. On the other hand, for 17 patients (8.6%), this variable was inapplicable according to age (Table 2).

With respect to patients' residence areas, 114 (57.9%) reported living in urban areas and three patients lived in indigenous territory of Rondonópolis. Only four notifications presented patients belonging to other municipalities, which are included to the same health region (southeast), according to the division of Mato Grosso Regions of Health.[7]

In our study, the included cases were distributed in 79 (33%) neighborhoods in the municipality of Rondonópolis. Geoprocessing analysis showed a high density of notified cases in three urban neighborhoods of the city, in the central and north, as shown in Figure 1.

According to clinical presentations data, only 46 (23.3%) forms had some information. Musculoskeletal disorders such as arthralgia, joint swelling, and myalgia were reported for 45 (22.8%) patients, who presented at least one of these symptoms, representing the main complaints. Fever (13.7%), headache (11.7%), itching (10%), and symptoms related to hematological disorders, such as rash and petechiae (12.6%), were also notified. Other described symptoms were ophthalmological (6.1%) and gastrointestinal (5.6%) manifestations (Table 3).

Experimental analyses were performed with a total of 179 serum samples (Table 4). Molecular assay revealed three (1.7%) patients infected with DENV. Additionally, 16 (8.9%) patients had positive results for ZIKV, and CHIKV RNA was not detected in any clinical serum samples. Therefore, a total of 19 patients tested positive in molecular assays performed by the study, of which 18 (94.7%) were women. Regarding the ZIKV serology, IgM was detected in 19 (10.6%) samples and IgG in 100 (55.8%).



Legend: maps of Brazil, state of Mato Grosso (MT) and the municipality of Rondonópolis (black) (A); spatial distribution of reported cases of ZIKV, DENV, and CHIKV by notification density among the urban neighborhoods in the municipality of Rondonópolis (B) during the ZIKV Brazilian epidemic (2015-2016).

Figure 1. Geographic location of study area.

Table 3. Clinical features of arboviruses of suspected cases in Rondonópolis, Brazil, during the ZIKV Brazilian epidemic (2015–2016).

	Frequency	
Clinical signs/symptoms	**n (197)**	**%**
Systemic		
Fever	27	13.7
Itching	20	10.1
Headache	23	11.7
Gastrointestinal		
Vomit		
Nausea	11	5.6
Abdominal pain		
Diarrhea		
Musculoskeletal		
Arthralgia		
Joint swelling	45	22.8
Myalgia		
Hematological		
Petechiae	25	12.6
Rash		
Ophthalmological		
Retro-orbital pain	12	6.1
Conjunctival hyperemia		

Table 4. Molecular and serological investigation of serum samples of arboviruses of suspected cases in Rondonópolis, Brazil, during the ZIKV Brazilian epidemic (2015–2016).

Clinical signs/ symptoms	Molecular detection Positive/n	Serological detection (ZIKV) Positive/n	
		IgM	IgG
DENV	3/179 (1.7%)	NA	NA
ZIKV	16/179 (8.9%)	19/179 (10.6%)	100/179 (55.8%)
CHIKV	ND	NA	NA

Legend: IgG: immunoglobulin G; IgM: immunoglobulin M; NA: not available; ND: not detected.

DISCUSSION

In this retrospective study, we assessed clinical, epidemiological, and laboratorial data of DENV, ZIKV, and CHIKV suspected cases in a Brazilian municipality located in southeastern MT, in the midwest region of Brazil. Such geographic area is endemic for DENV, with the concomitant occurrence of ZIKV and CHIKV. Our study reveals unprecedented data for arboviruses in this geographic region during the introduction of ZIKV and CHIKV in Brazil, 2015-2016. Molecular arbovirus investigation was performed during the same period, in Cuiabá, the state capital of MT, which is a distant region.[8]

Rondonópolis has approximately 236,000 inhabitants, and is the reference point to 18 other cities belonging to the Southeast Health region. During the period 2015–16, the city reported 8,597 notifications of DENV, 535 of ZIKV, and 70 of CHIKV fever, with a high incidence of DENV and ZIKV fever during the same period. In 2015–16, ZIKV and CHIKV fever cases were reported in about half of all Brazilian municipalities, while probable DENV cases were reported in all of them. Therefore, Brazil and consequently MT registered an expressive number of DENV, ZIKV, and CHIKV notifications due to the introduction and expansion of the recently emerging arboviruses associated with the persistence and endemicity of DENV. And the increased number of notifications occurred mainly during rainy seasons, according to SINAN notifications.[7,9-13] Our data supported this observation, with the highest number of cases (61%) detected by molecular tests reported between December 2015 and April 2016, with poor impact in reducing cases through educational campaigns for vector control implemented by Brazilian health authorities.

Following the introduction of ZIKV and the beginning of the outbreak in 2015 in Brazil, accurate laboratorial diagnostics were not available for MT, as in most parts of the country. The first positive confirmed results were reported only in February 2016 by the epidemiological surveillance program of the Department of Health of Mato Grosso. On the other hand, ZIKV was detected in a human sample collected in the municipality of Tapurah, northern MT, in August 2015.[8] The first positive cases in pregnant women were also confirmed in February 2016 from Primavera do Leste, a municipality belonging to the same health region of Rondonópolis, reinforcing viral circulation in this area.[13] However, the first suspected case of CZS in this region probably occurred in June 2015, which would confirm the circulation of ZIKV in MT in the middle of that year.[4] In the same way, the first laboratory-confirmed cases of CHIKV fever were reported only in March 2016.[7]

In this regard, adequate filling of notification forms and protocols available by Brazilian health authorities is essential for implementing epidemiological surveillance programs, especially considering the introduction of new arboviruses in DENV endemic areas, as observed in the CHIKV and ZIKV outbreak cases in recent years.[5] Therefore, the high number of variables missing in different fields of the notification forms assessed in our study highlight the need for proper filling of notification forms for suspected cases, as clinical diagnosis was essential for introducing these arboviruses in Brazil, mainly due to the lack of serological or molecular diagnoses.

As for socio-demographic analyses, Female patients accounted for almost 63% of the total cases in our study, and eight of them were pregnant. A similar rate is commonly observed in other surveys, probably because women are more likely to seek healthcare compared to men, at least for arbovirus investigation. This phenomenon could also be explained by a greater risk of exposure to mosquito bites because of women domestic costumes. Other relevant fact about these data can be closely related to the protocol established by Brazilian authorities, which focused on women, mainly during pregnancy, because of the occurrence of CZS, especially during 2015–16. This fact may have motivated females to search for more healthcare, thus resulting in a greater number of positive cases, as observed in our study.[11,14] A larger number of notifications was observed for patients in the age group of 19–59 years old, which represents the economically more active population. Although professional occupation was not assessed in the study,

this profile represents important insight for the local economy, as arboviruses affect patient productivity, with a critical impact on daily work routines. Similar patterns were shown in other profile epidemiological studies conducted in Brazil.[11,15]

It was observed that notifications were concentrated in urban areas with high population density and hence higher risk of infection. This fact reinforces and corroborates the urban features of DENV, ZIKV, and CHIKV, transmitted by anthropophilic mosquitoes to humans, which act as amplification hosts for these arboviruses critical to public health.[16]

Although only three notifications were reported in indigenous territory, these rural areas are close to urban areas of Rondonópolis and may represent a potential risk zone for future outbreaks, depending on ecological conditions. Therefore, these suspected cases highlight the importance of consider indigenous territory in the municipality epidemiological surveillance programs.

Epidemiological features and climatic and ecological conditions, such as rainfall periods associated with high temperatures, may predict arboviral epidemics. These features, accompanied by disorderly urban growth, overpopulation, and precarious sanitary conditions, combined with inefficient vector control programs, result in more mosquito breeding grounds and provide conducive conditions for increased proliferation of infectious disease vectors, such as arboviruses. In this regard, low socioeconomic status and less education levels are both important for individuals and consequently familiar risk to contract these febrile syndromes.[17,18] Therefore, due to the accelerated and disordered urbanization process of the municipality of Rondonópolis, the notable social, economic, and environmental differences among all urban neighborhoods can influence the high incidence of these diseases.[16,19]

The three arboviral diseases investigated in this study are closely related and cause DENV-like clinical signs and symptoms. Moreover, about 80% of ZIKV cases are asymptomatic and may thus hinder differential clinical diagnosis, resulting in arbovirus misclassification. Therefore, the concomitant circulation of ZIKV, CHIKV, and other arboviruses in an area endemic to DENV, where laboratory tests are not always available for prompt confirmation, is a challenge for public health authorities and especially for health professionals, which in turn interfere with obtaining accurate diagnosis.[8,20-22]

In this scenario, it is important that clinical assessment is followed by laboratory diagnosis, especially molecular assays, which provide a specific diagnosis since the onset of symptoms. Serological assays may present the possibility of cross-reaction and false positive results for arboviruses with the synthesis of cross-reactive antibodies in patients previously exposed to some heterologous flaviviruses, often leading to inconclusive serology diagnostics. Furthermore, serological assays do not determine which DENV serotype is indeed circulating, which is very relevant, mainly in epidemic situations.[11,6]

It is important to point out that molecular and serological assays may be performed at different stages of the arboviral disease. Molecular assays may only be feasible during viremia stages, approximately five days after symptom onset. On the other hand, serology can be applicable after antibody synthesis, which is detectable at the end of the viremia stage.[6] Thus, our results showed one positive DENV sample in the molecular assay with the presence of ZIKV IgM antibodies, probably due to cross-reactivity. In addition, 14 positive ZIKV IgM were negative by molecular test. Furthermore, IgM was not detected in other 12 from 16 ZIKV RT-qPCR positive samples, probably because antibody synthesis was not completed or under the ELISA detection limits. Therefore, only four samples reached concomitantly serological (IgM) and molecular positive diagnosis, which combined with the high number of IgG positive results reinforce the possibility of cross-reaction, since the virus had just introduced into the region, showing that serological diagnosis is neither adequate nor timely.

New viruses recently discovered in the Pantanal biome in MT are indicators of the possibility of future interactions and compromise of human health.[23] Interestingly, it was observed that only 2% (4) of patients were submitted to some laboratorial diagnostic test by public health services in Rondonópolis during clinical assessment, and all were negative for acute infection by serological analysis. However, about 10.6% (19) of 179 sampled patients had positive RNA detection in our molecular investigation (IgM). Similar rates have been observed in related surveys.[24]

In this context, the negative cases may have been probably caused by other pathogens not investigated during clinical follow-up. Considering the total number of reported notifications during the studied period, it is possible to infer that epidemiological and clinical criteria alone are insufficient for accurate diagnoses. Furthermore, accurate laboratory diagnosis may have implications for patient management and clinical evolution, such as effective treatment, and this highlights the importance of molecular assays for early detection and definitive confirmation of febrile syndrome etiologies.[25]

It is important to address the limitations of this study, which were related to the quality of data obtained from patients' SINAN forms, with high level of incomplete information. In addition to this, there is the possibility of other infectious etiologies since the survey was designed only for DENV, ZIKV, and CHIKV molecular detection and for ZIKV serological investigation. Moreover, the samples were collected between 2015–16, and molecular analyses were performed only in 2019–20, indicating the possibility of viral RNA degradation.

In conclusion, our study provides singular local research concerning clinical and laboratorial assessment of suspected arboviruses infected patients during the first outbreak of ZIKV and CHIKV in Brazil, in a region that has shown a high incidence of DENV cases, representing a relevant contribution to understanding the concomitant occurrence of these acute febrile syndromes.

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AUTHOR'S CONTRIBUTIONS

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ORIGINAL ARTICLE

Profile of post-exposure anti-rabies treatments to wild mammals in a health region, Pernambuco, Brazil, 2014-2020

Perfil dos atendimentos antirrábicos pós-exposição a mamíferos silvestres em região de saúde, Pernambuco, Brasil, 2014-2020

Perfil de la atención antirrábica post-exposición a mamíferos silvestres en una región de salud, Pernambuco, Brasil, 2014-202

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Corresponding Author:
Emília Carolle Azevedo de Oliveira
emiliacarolle@hotmail.com

Address: Instituto Aggeu Magalhães – Av. Professor Moraes Rego, s/n – Cidade Universitária – Recife/PE – CEP 50.740-465.

Laysa Lindaura Lau Rocha Cordeiro[1];
Maria Olívia Soares Rodrigues[2];
Louisiana Regadas de Macedo Quinino[1];
Francisco Duarte Farias Bezerra[2];
Raylene Medeiros Ferreira Costa[2];
Emília Carolle Azevedo de Oliveira[1];

[1] *Fundação Oswaldo Cruz, Instituto Aggeu Magalhães, Recife, PE, Brazil.*
[2] *State Health Department of Pernambuco, Recife, PE, Brail.*

ABSTRACT

Justification and Objectives: since 2016, Brazil has not registered any cases of human rabies transmitted by dogs, with the disease now primarily associated with wild mammals. In Pernambuco, the last reported case occurred in 2017 in Recife. Considering the reporting of anti-rabies treatments as a crucial tool for the epidemiological surveillance of rabies, this study aimed to analyze post-exposure anti-rabies treatments related to wild mammals in the First Health Region of Pernambuco between 2014 and 2020. **Methods:** a descriptive, analytical, and cross-sectional study was conducted on human anti-rabies treatments reported in the Notifiable Diseases Information System. Data were processed using Excel, with the chi-square test assuming $p < 0.05$. A qualitative assessment was performed to identify duplicate records in different health units. **Results:** a total of 799 human anti-rabies treatments were identified, primarily in adults (20-34 years) and mixed-race individuals, with no statistical difference between sexes. Bats were the most involved species. The accidents mainly occurred through bites, on hands and feet, with single and superficial wounds. Most prophylactic recommendations were serum-vaccination. A total of 64 duplicate treatments were recorded in different health units. **Conclusion:** although most post-exposure prophylactic recommendations were appropriate, anti-rabies accidents involving wild mammals are classified as severe. This underscores the importance of strictly adhering to the prophylactic protocol established by the health authority. The identification of duplicate records also highlights the need for improvements in the integration of health systems and the training of professionals to ensure efficiency in case reporting and treatment.

Keywords: *Epidemiology. Rabies. Post-Exposure Prophylaxis. Wild Mammals.*

RESUMO

Justificativa e Objetivos: desde 2016, o Brasil não registra casos de raiva humana transmitida por cães, com a doença agora associada principalmente a mamíferos silvestres. Em Pernambuco, o último caso ocorreu em 2017, em Recife. Considerando a notificação dos atendimentos antirrábicos uma ferramenta crucial para a vigilância epidemiológica da raiva, este estudo teve como objetivo analisar os atendimentos antirrábicos pós-exposição a mamíferos silvestres na Primeira Região de Saúde de Pernambuco entre 2014 e 2020. **Métodos:** estudo descritivo, analítico e transversal dos atendimentos antirrábicos humanos notificados no Sistema de Informação de Agravos de Notificação. Os dados foram processados utilizando o *software Excel*, com o teste qui-quadrado assumindo $p < 0,05$. Uma avaliação qualitativa foi feita para identificar registros duplicados em diferentes unidades de saúde. **Resultados:** foram identificados 799 atendimentos antirrábicos humanos, principalmente em adultos (20-34 anos) e pessoas pardas, sem diferença estatística entre os sexos. O morcego foi a espécie mais envolvida. Os acidentes ocorreram principalmente por mordedura, em mãos e pés, com ferimentos únicos e superficiais. A maioria das indicações profiláticas foi a soro-vacinação. Foram registradas 64 duplicidades de atendimentos em unidades de saúde distintas. **Conclusão:** embora a maioria das indicações profiláticas pós-exposição tenha sido adequada, os acidentes antirrábicos envolvendo mamíferos silvestres são classificados como graves. Isso destaca a importância do cumprimento rigoroso do protocolo profilático estabelecido pela autoridade sanitária. As duplicidades nos registros apontam para a necessidade de melhorias na integração dos sistemas de saúde e na capacitação dos profissionais para garantir a eficiência na notificação e tratamento dos casos.

Descritores: *Epidemiologia. Raiva. Profilaxia Pós-Exposição. Mamíferos Silvestres.*

RESUMEN

Justificación y Objetivos: desde 2016, Brasil no ha registrado casos de rabia humana transmitida por perros, con la enfermedad ahora asociada principalmente a mamíferos silvestres. En Pernambuco, el último caso ocurrió en 2017, en Recife. Considerando la notificación de los atendimientos antirrábicos como una herramienta crucial para la vigilancia epidemiológica de la rabia, este estudio tuvo como objetivo analizar los atendimientos antirrábicos post-exposición a mamíferos silvestres en la Primera Región de Salud de Pernambuco entre 2014 y 2020. **Métodos:** se realizó un estudio descriptivo, analítico y transversal de los atendimientos antirrábicos humanos notificados en el Sistema de Información de Agravios de Notificación. Los datos fueron procesados utilizando el *software Excel*, con la prueba de chi-cuadrado asumiendo $p < 0,05$. Se realizó una evaluación cualitativa para identificar registros duplicados en diferentes unidades de salud. **Resultados:** se identificaron 799 atendimientos antirrábicos humanos, principalmente en adultos (20-34 años) y personas pardas, sin diferencia estadística entre los sexos. El murciélago fue la especie más involucrada. Los accidentes ocurrieron principalmente por mordedura, en manos y pies, con heridas únicas y superficiales. La mayoría de las indicaciones profilácticas fueron suero-vacunación. Se registraron 64 duplicidades de atendimientos en distintas unidades de salud. **Conclusión:** aunque la mayoría de las indicaciones profilácticas post-exposición fueron adecuadas, los accidentes antirrábicos que involucran mamíferos silvestres se clasifican como graves. Esto destaca la importancia del cumplimiento riguroso del protocolo profiláctico establecido por la autoridad sanitaria. La identificación de duplicidades en los registros también señala la necesidad de mejoras en la integración de los sistemas de salud y en la capacitación de los profesionales para garantizar la eficiencia en la notificación y tratamiento de los casos.

Palabras Clave: *Epidemiología. Rabia. Profilaxis Post-Exposición. Mamíferos Silvestres.*

INTRODUCTION

Rabies is an anthropozoonosis of high relevance in public health due to its high lethality, resulting in more than 60,000 annual deaths worldwide.[1] Caused by the virus of the genus *Lyssavirus*, of the family *Rhabdoviridae*, present in the saliva of infected animals, the current transmission has been significantly associated with the hematophagous bat.[2-4] Since 2016, there have been no reports of human rabies transmitted by dogs in Brazil, indicating a change in the epidemiological profile of the disease, with cases being predominantly transmitted by wild mammals or resulting from their antigenic variants, such as the vampire bat variant (AgV3) and variants of *Callithrix jacchus* and wild canids.[5] Rabies occurs most frequently in northern and northeastern Brazil, mainly affecting children and adolescents in rural areas.[6]

In Pernambuco, between 1990 and 2023, 45 cases of human rabies were reported, with the last fatal case confirmed in the city of Recife, in 2017, transmitted by a cat infected with AgV3.[7,8] As for anti-rabies care after exposure to wild mammals, approximately 35% of reports occurred in Recife and in the municipalities of the Metropolitan Region of Recife (MRR), between 2011 and 2017,[9] belonging to the First Health Region of Pernambuco. Most of the care involved accidents with bats and primates.[9]

Although it has a fatality rate of almost 100%,

rabies is a vaccine-preventable disease. Human rabies prophylaxis is offered free of charge by the Brazilian Health System, with the recommendation of administering serum and vaccine (or re-exposure) in cases of accidents involving wild mammals.[10,11] Moreover, human rabies accidents must be immediately reported by healthcare services, even when treatment with immunobiological agents is not recommended. These actions, together with rabies vaccination campaigns for dogs and cats and health education initiatives, contribute to reducing the incidence of the disease and the effectiveness of rabies elimination programs, strengthening health systems, especially surveillance systems.

Considering the above, this study aimed to analyze anti-rabies care after exposure to wild mammals in the First Health Region of Pernambuco between 2014 and 2021.

METHODS

This is a descriptive and inferential study, with a cross-sectional design, of anti-rabies care after exposure to wild mammals reported in the Notifiable Diseases Information System (In Portuguese, *Sistema de Informação de Agravos de Notificação* - SINAN), between 2014 and 2020, in the First Health Region of Pernambuco.

The state of Pernambuco is made up of 184 municipalities and the Fernando de Noronha Archipelago, administratively organized into 12 health regions. The First Health Region is the most populous (4,208,906 inhab.; 3,721.3 km^2) and with the greatest supply of healthcare services, being made up of the municipalities of Abreu e Lima, Araçoiaba, Cabo de Santo Agostinho, Camaragibe, Chã Grande, Chã de Alegria, Glory of Goitá, the Archipelago of Fernando de Noronha, Igarassu, Ipojuca, Itamaracá, Itapissuma, Jaboatão dos Guararapes, Moreno, Olinda, Paulista, Pombos, Recife, São Lourenço da Mata and Vitória de Santo Antão.[12]

The data were obtained from the Coordination of Zoonoses and Accidents due to Venomous Animals of the State Health Department of Pernambuco on March 24, 2023. All cases reported in the First Health Region as "human anti-rabies care" were considered. The records were selected based on year of exposure (2014-2020) and attacking animal species, covering chiroptera (bats), primates (monkeys) and foxes, the wild mammals of greatest importance in the epidemiological cycle of rabies in Brazil.[11] Duplicates by SINAN registration number and cases reported with animals of other species and outside the period analyzed were excluded.

The selected variables were classified into three categories: sociodemographic profile; epidemiological history; and treatment. The sociodemographic profile included the variables municipality of reporting, sex, age, race/color, education level, and area of residence. In the epidemiological history, type of exposure to the rabies virus, wound site, type of wound, date of exposure, history of anti-rabies treatment, attacking animal species and animal condition for the purposes of treatment conduct were considered. In the treatment category, treatment recommended, animal final condition after the observation period, interruption of treatment, reason for interruption, active search for the health unit of patients who abandoned treatment and additional observations were analyzed.

Descriptive statistical analysis was performed using absolute and relative frequencies, mean, standard deviation (SD) and incidence rate. The total annual incidence rate of cases was calculated as the ratio between the absolute number of registered cases (2014-2020) and the estimated population of the First Health Region, according to the Brazilian Institute of Geography and Statistics of 2010. The incidence rate by animal species was calculated as the ratio between the absolute number of cases per species (2014-2020) and the estimated population for each species, both multiplied by 100,000.

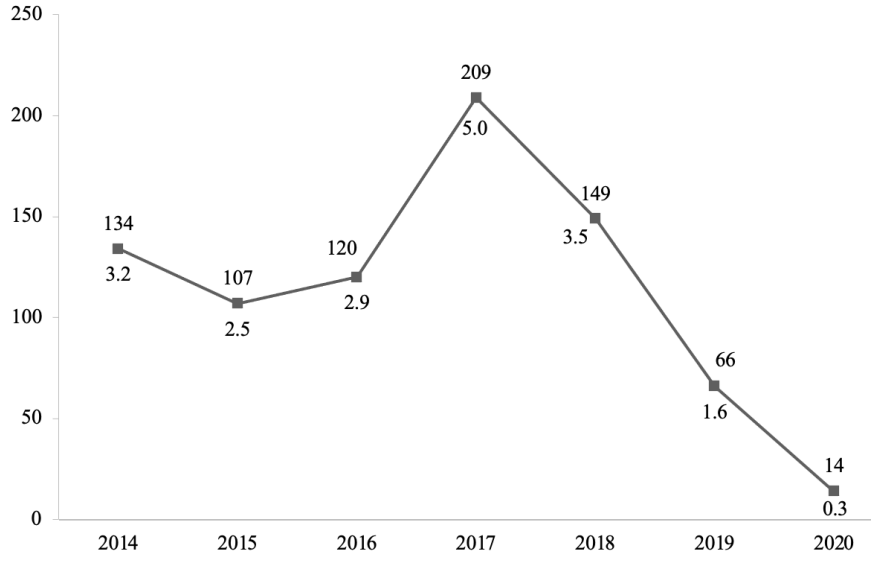
The chi-square test was used to test the association between the variables of interest during the study period, related to sociodemographic characteristics, wound characteristics and animal species, considering a 95% Confidence Interval and a significance level of <0.05. All database processing, statistical tests, graphs and tables were performed in Microsoft Excel 365.

As part of qualitative analysis, the recommendation of post-exposure rabies prophylaxis with serum and vaccine was classified as "adequate", following the current health authority recommendations.[10,11] The re-exposure procedure was not assessed for this classification, as it requires a more detailed investigation that correlates the variables of history of anti-rabies treatment, period of completion (up to 90 days/after 90 days) and number of doses applied. Furthermore, all post-exposure prophylactic measures for wild mammals that were not recommended were classified as "inadequate". An individual and qualitative analysis was also performed on duplicate records of the same exposure reported in more than one health unit, aiming to identify consistency in the recommendation of post-exposure anti-rabies treatment.

This research was conducted in accordance with the ethical standards defined by Resolutions 466/2012, 510/2016 and 580/2018 of the Ministry of Health, and was approved by the *Instituto Aggeu Magalhães* (IAM) (Fiocruz/PE) Research Ethics Committee, under Opinion 5,873,716 and Certificate of Presentation for Ethical Consideration 65555522.7.0000.5190.

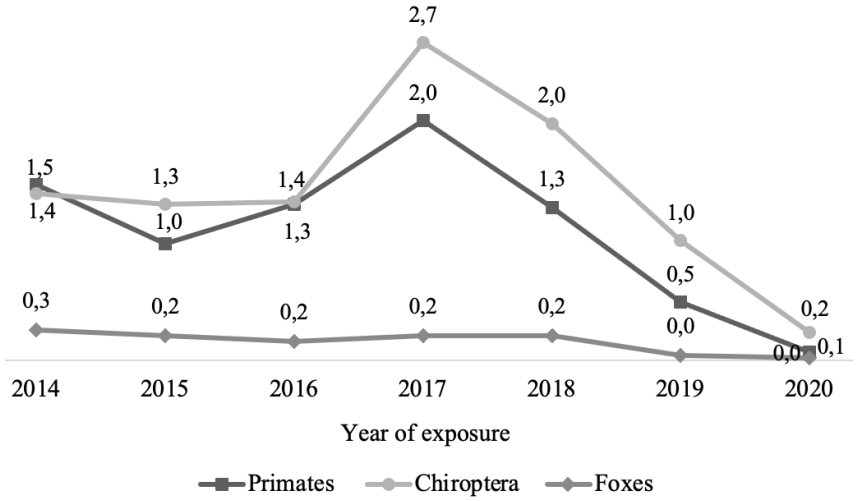
RESULTS

Between 2014 and 2020, the First Health Region reported 799 human anti-rabies treatments after exposure to wild mammals. In total, 17 municipalities recorded anti-rabies treatment after exposure to bats, primates or foxes, mainly in the city of Recife (n=499; 62.5%). Together, the number of cases reported in the cities of Vitória de Santo Antão, Paulista, Jaboatão dos Guararapes and Olinda totaled 24.6%. The average number of annual cases was approximately 114 (SD = 62), with the highest number of reports recorded in 2017 (n = 209; 5.0/100,000 inhab.), and the lowest in 2020 (n = 14; 0.3/100,000 inhab.) (Figure 1).



Source: SINAN data. Prepared by the authors.

Figure 1. Time series of post-exposure anti-rabies care to wild mammals according to the number and total incidence rate. First Health Region, Pernambuco, 2014 to 2020.



Source: SINAN data. Prepared by the authors.

Figure 2. Incidence rate of anti-rabies care after exposure to bats, primates and foxes. First Health Region, Pernambuco, 2014 to 2020.

The annual average number of accidents involving bats, primates and foxes was 60.7 (SD = 32.5), 46.6 (SD = 27.6) and 6.9 (SD = 3.8), respectively. The incidence rate of care in the population due to accidents with foxes was highest in 2014 (n = 11; 0.3/100,000 inhab.), whereas for bats (n = 114; 2.7/100,000 inhab.) and primates (n = 86; 2.0/100,000 inhab.) the peak occurred in 2017 (Figure 2).

The distribution by sex was homogeneous, with 51.1% of cases involving men and 48.9% involving women. The most affected age group was 20 to 34 years (24.8%), with the majority of people being mixed-race (36.4%). Records with the race/color and education fields not filled in or marked as unknown were quite representative, totaling, respectively, 43.6% and 57.7%. The majority of individuals lived in urban areas (87.4%) (Table 1).

In relation to sex and race/color, mixed-race people were the most affected, specifically females (χ^2 = 15.2; p = 0.004). The association between sex and age group (χ^2 = 12.1; p = 0.208) and sex and education (χ^2 = 9.4; p = 0.307) was not significant.

Accidents occurred mainly due to biting (79%), with a higher frequency on hands and feet (47.8%). Single wounds were the most frequently reported (63.7%), as were superficial wounds (59.6%). In general, the recommendation of serum and vaccine was observed in 81.1% of cases, and the conduct was classified as adequate. Re-exposure conduct was observed in 1.3% of cases (n=10); of these, only eight records contained

Table 1. Sociodemographic profile of anti-rabies care after exposure to wild mammals. First Health Region, Pernambuco, 2014 to 2020.

SOCIODEMOGRAPHIC PROFILE				
	Female n (%)	**Male n (%)**	**Total n (%)**	***p*[4]**
Age group				0.208
< 1 year	8 (2)	11 (2.7)	19 (2.4)	
1 to 4 years	15 (3.8)	17 (4.2)	32 (4)	
5 to 9 years	28 (7.2)	30 (7.4)	58 (7.3)	
10 to 14 years	18 (4.6)	27 (6.6)	45 (5.6)	
15 to 19 years	28 (7.2)	33 (8.1)	61 (7.6)	
20 to 34 years	90 (23)	108 (26.5)	198 (24.8)	
35 to 49 years	84 (21.5)	97 (23.8)	181 (22.7)	
50 to 64 years	84 (21.5)	58 (14.2)	142 (17.8)	
65 to 79 years	27 (6.9)	23 (5.6)	50 (6.3)	
80 and older	9 (2.3)	4 (1)	13 (1.6)	
Race/color				0.004
White	63 (16.1)	68 (16.7)	131 (16.4)	
Black	6 (1.5)	19 (4.7)	25 (3.1)	
Yellow	0 (0)	1 (0.2)	1 (0.1)	
Mixed-race	148 (37.9)	143 (35)	291 (36.4)	
Indigenous	1 (0.3)	2 (0.5)	3 (0.4)	
Ignored or blank	173 (44.2)	175 (42.9)	348 (43.6)	
Education				0.307
Illiterate	0 (0)	2 (0.5)	2 (0.3)	
Incomplete 1st to 4th grade of elementary school[1]	15 (3.8)	23 (5.6)	38 (4.8)	
Complete 4th grade of elementary school[1]	4 (1)	6 (1.5)	10 (1.3)	
Incomplete 5th to 8th grade of elementary school[2]	13 (3.3)	20 (4.9)	33 (4.1)	
Complete elementary school[2]	12 (3.1)	7 (1.7)	19 (2.4)	
Incomplete high school[3]	9 (2.3)	7 (1.7)	16 (2)	
Complete high school[3]	41 (10.5)	44 (10.8)	85 (10.6)	
Incomplete higher education	10 (2.6)	7 (1.7)	17 (2.1)	
Complete higher education	24 (6.1)	22 (5.4)	46 (5.8)	
Ignored or blank	229 (58.6)	232 (56.9)	461 (57.7)	
Not applicable	34 (8.7)	38 (9.3)	72 (9)	
Area of residence				0.436
Urban	349 (89.3)	349 (85.5)	698 (87.4)	
Rural	17 (4.3)	22 (5.4)	39 (4.9)	
Ignored or blank	25 (6.4)	37 (9.1)	62 (7.8)	

Note: [1]Former primary or 1st grade; [2]Former high school or 1st grade; [3]Former high school or 2nd grade; [4]The "ignored", "not applicable" and blank fields were not considered in the chi-square test. Source: SINAN data. Prepared by the authors.

information on history of post-exposure anti-rabies treatment (Table 2).

The type of exposure (χ^2 = 20.6; p = 0.008), wound site (χ^2 = 43.9; p = 0.000), wound (χ^2 = 22.7; p = 0.000) and type of wound (χ^2 = 15.5; p = 0.004) were statistically significant between species, as was treatment recommended (χ^2 = 53.2; p = 0.000 (Table 2). Although biting was predominant in accidents involving the three species, scratching was also significant, followed by indirect contact, for bats, and licking, for primates and foxes. Hands and feet had the highest frequency of wounds, followed by upper limbs and head/neck in both bat and primate accidents, whereas lower limbs were the second most frequently reported site in fox accidents. Wound-free exposures were observed for both bats and primates.

More than half of animals were declared dead or missing (54.4%) when the "animal condition" field was filled in. Similarly, regarding animal final condition, clinical diagnosis was negative in most cases (66.7%). Among the few cases that underwent laboratory diagnosis (3% of the total), 0.5% tested positive for rabies (Table 2).

By qualitatively analyzing duplicate records, it was possible to identify that 64 cases of the same accident were reported in more than one health unit. The recommendation for treatment with serum and vaccine prevailed in the three care units. However, conducts classified as inadequate, such as observation and vaccine (1st unit - 1.6%) and only vaccine (1st unit - 7.8%; 2nd unit - 1.6%), were also recommended (Table 3).

Table 2. Anti-rabies care after exposure to wild mammals according to epidemiological history and treatment. First Health Region, Pernambuco, 2014 to 2020.

	ATTACKING ANIMAL SPECIES				
	Primate n (%)	**Chiroptera n (%)**	**Fox n (%)**	**Total n (%)**	***p***
Type of exposure					0.008
Indirect contact	6 (1.8)	29 (6.8)	0 (0)	35 (4.3)	
Scratching	32 (9.6)	53 (12.5)	5 (9.8)	90 (11.1)	
Licking	9 (2.7)	10 (2.4)	1 (2)	20 (2.5)	
Biting	278 (83.5)	316 (74.4)	45 (88.2)	639 (79)	
Other	8 (2.4)	17 (4)	0 (0)	25 (3.1)	
Site					0.000
Mucosa	5 (1.5)	17 (3.9)	0 (0)	22 (2.6)	
Head/neck	59 (17.4)	64 (14.6)	1 (1.8)	124 (14.9)	
Hands/feet	183 (53.8)	193 (44.2)	22 (40)	398 (47.8)	
Trunk	13 (3.8)	26 (5.9)	5 (9.1)	44 (5.3)	
Upper limbs	57 (16.8)	78 (17.8)	11 (20)	146 (17.5)	
Lower limbs	23 (6.8)	59 (13.5)	16 (29.1)	98 (11.8)	
Wound					0.000
Single	197 (64.6)	257 (64.1)	26 (54.2)	480 (63.7)	
Multiple	103 (33.8)	112 (27.9)	22 (45.8)	237 (31.4)	
No wound	5 (1.6)	32 (8)	0 (0)	37 (4.9)	
Type of wound					0.004
Deep	129 (43.3)	120 (33.2)	23 (46.9)	272 (38.4)	
Superficial	160 (53.7)	238 (65.9)	24 (49)	422 (59.6)	
Lacerating	9 (3)	3 (0.8)	2 (4.1)	14 (2)	
Animal condition (treatment conduct)					0.000
Dead/missing	128 (44.1)	235 (63)	19 (48.7)	382 (54.4)	
Rabid	2 (0.7)	11 (2.9)	0 (0)	13 (1.9)	
Healthy	75 (25.9)	20 (5.4)	10 (25.6)	105 (15)	
Suspicious	85 (29.3)	107 (28.7)	10 (25.6)	202 (28.8)	
Treatment recommended					0.000
Pre-exposure	14 (4.4)	2 (0.5)	2 (4.3)	18 (2.3)	
No treatment required	2 (0.6)	8 (1.9)	0 (0)	10 (1.3)	
Animal observation	2 (0.6)	3 (0.7)	0 (0)	5 (0.6)	
Observation + vaccine	31 (9.7)	10 (2.4)	6 (12.8)	47 (6)	
Vaccine	21 (6.6)	28 (6.7)	9 (19.1)	58 (7.4)	
Serum + vaccine	248 (77.7)	358 (85.9)	29 (61.7)	635 (81.1)	
Re-exposure scheme	1 (0.3)	8 (1.9)	1 (2.1)	10 (1.3)	
Animal final condition					0.545
Rabies negative (clin.)	72 (67.3)	53 (63.1)	11 (84.6)	136 (66.7)	
Rabies negative (lab.)	2 (1.9)	3 (3.6)	0 (0)	5 (2.5)	
Rabies positive (clin.)	0 (0)	2 (2.4)	0 (0)	2 (1)	
Rabies positive (lab.)	0 (0)	1 (1.2)	0 (0)	1 (0.5)	
Dead/euthanized/no diagnosis	33 (30.8)	25 (29.8)	2 (15.4)	60 (29.4)	
Interruption of treatment					0.965
Yes	28 (14.2)	30 (14)	4 (16)	62 (14.2)	
No	169 (85.8)	184 (86)	21 (84)	374 (85.8)	
Reason for interruption					0.603
Recommendation of health unit	11 (39.3)	9 (30)	1 (25)	21 (33.9)	
Abandonment	16 (57.1)	17 (56.7)	3 (75)	36 (58.1)	
Transfer	1 (3.6)	4 (13.3)	0 (0)	5 (8.1)	
Active search					0.435
Yes	8 (61.5)	10 (66.7)	3 (100)	21 (67.7)	
No	5 (38.5)	5 (33.3)	0 (0)	10 (32.3)	

Source: SINAN data. Prepared by the authors.

Table 3. Duplicate reports in different health units. First Health Region, Pernambuco, 2014 to 2020.

	DUPLICITY IN DIFFERENT HEALTH UNITS		
	1st Health Unit n (%)	**2nd Health Unit n (%)**	**3rd Health Unit n (%)**
Treatment recommended			
Observation + vaccine	1 (1.6)	0 (0)	0 (0)
Vaccine	5 (7.8)	1 (1.6)	0 (0)
Serum + vaccine	56 (87.5)	63 (98.4)	6 (100)
Not filled in	2 (3.1)	0 (0)	0

Source: SINAN data. Prepared by the authors.

DISCUSSION

During the period analyzed, 799 human anti-rabies treatments were reported after exposure to wild mammals, predominantly in the city of Recife. In the sociodemographic profile, mixed-race people were the most affected, with a higher prevalence among women, young people and adults with a high school education, and residents of urban areas. Among the three species studied, exposure to bats was the most reported. Anti-rabies care was mainly due to bites, affecting hands and feet, with single and superficial lesions. The anti-rabies prophylaxis recommended was appropriate for the type of exposure in most cases, although some inadequate recommendations were also identified.

The year 2017 recorded the highest number of reports, similar to that observed in an analysis of rabies accidents involving wild mammals for the state of Pernambuco.[9] That year, the city of Recife reported the last human rabies death in the state, with the source of infection being a stray cat infected by the vampire bat variant, in a phenomenon known as "spillover".[7,8,13] Underreporting may explain the sharp drop in case registrations in the final years of the period analyzed. This may be related to several factors, including the lack of adequate training of healthcare professionals to identify and report cases, changes in surveillance policies, and the possible reduction in demand for care due to the population's lack of knowledge about the importance of post-exposure treatment. Furthermore, the COVID-19 pandemic may have impacted healthcare services' ability to effectively report cases in recent years, diverting resources and attention to controlling the new health emergency.

Other positive factors that may explain the findings include improvements in prevention measures, such as vaccination campaigns and rabies control in domestic and wild animals as well as increased public awareness and better training of healthcare professionals. On the other hand, negative factors such as reduced active surveillance, lack of resources and demographic changes may also have contributed to the variations in case records.

The race/color and education fields were substantially ignored or not filled in in this study, reflecting the incompleteness of the database. These criteria are fundamental to delineating the epidemiological profile of the population, allowing the identification of vulnerable groups and inequalities in access to information and healthcare services. The lack of such data may result in less knowledge about the disease and the need for post-exposure rabies care to wild mammals, in addition to highlighting access barriers from the perspective of racial inequities.[14,15]

In this study, accidents involving bats were the most representative, with an average of 1.4 accidents per 100,000 inhabitants in the First Health Region. When analyzing the incidence rate of attacks by bites from animals that transmit rabies in Brazil (2008-2016), Benavides *et al.*[16] found results that ranged from 0.6 to 2.3 bites per 100,000 inhabitants in accidents with wild mammals, values lower than those observed in dog and cat bites. The authors, however, emphasize the importance of careful interpretation of these findings, since both underreporting and the geographic occurrence of attacks, such as outbreaks in rural areas and indigenous communities,[2,17] may influence the results, making them elevated in some locations.[16]

Biting was the main type of exposure found, being commonly reported in the literature.[6,18-20] Hands and feet were the most frequently attacked areas, probably because they were used in an attempt to defend themselves against attacks/accidents or because they were extremities, supporting other authors. [18,19,21,22] Recently, a man died after being infected with the rabies virus in the state of Ceará. The symptoms occurred concomitantly with the COVID-19 infection, two months after being bitten on the right wrist by a marmoset. The patient did not receive post-exposure rabies prophylaxis, and the diagnosis was confirmed post-mortem by direct immunofluorescence. [23]

Single and superficial wounds were the most reported for the three species, in disagreement with an analysis carried out on post-exposure anti-rabies care for wild mammals in the state of Pernambuco (2011-2017), where deep wounds were the most reported.[9]

Post-exposure rabies prophylaxis with serum and vaccine was the most recommended by healthcare professionals, in accordance with the protocol established by the Ministry of Health for accidents with bats or any other species of wild mammal.[10,11] For primates, observation and vaccination were the second most common treatment recommendations, while for bats and foxes, only vaccination was recommended. In addition to being incoherent and inconsistent, the recommendation to observe the animal (whether a dog or cat) or to dispense treatment in

cases involving bats and primates represents a weakness in the service offered to public health, considering the lethality of the disease. Several factors may be associated with inadequate recommendations for anti-rabies prophylaxis after exposure to wild mammals, such as the epidemiological transition of the disease in recent years, professionals' lack of knowledge of current immunological protocol, lack of training on the subject, high turnover of professionals in healthcare services and even low provision of health education for the population.[24,25]

Abandonment was the main reason given for interrupting treatment, and it is important to consider the possibility that the patient completed the prophylactic regimen in a different health unit from the one where the patient was first treated, resulting in duplicate records in non-integrated healthcare services. Interruption of treatment on the recommendation of the health unit was observed in a considerable number of reports, with the protocol being inappropriate for the type of accident analyzed (wild mammals).

In total, it was possible to identify 64 duplicate records for the same exposure in up to three different health units. Analyzing the "observations" field, it was identified that some patients were referred for human anti-rabies serum (not available in the first consultation) and for subsequent doses, generating duplicates due to the lack of communication and integration between the reporting units. The recommendation of serum and vaccine also prevailed in the different consultations.

The analysis of post-exposure rabies care for wild mammals in the First Health Region of Pernambuco is particularly relevant, as this is the most populous region of the state and has the largest supply of healthcare services. Between 2011 and 2017, Pernambuco reported 6,363 human rabies care involving wild mammals,[9] with most reports occurring in the MRR (35.1%) and *agreste* (23.7%).

The municipalities of the MRR are part of the First Health Region, which frequently meets the demand of other regions, due to its robust health infrastructure.[12] Therefore, the results of this study provide valuable insights for epidemiological surveillance, planning public health actions and improving responses to rabies accidents, not only in the First Health Region, but potentially throughout the state of Pernambuco and similar regions.

This study used secondary data, which may present limitations regarding data underreporting, incompleteness and inconsistency, which may trigger information biases. Correctly filling out investigation forms is essential to guide the rabies prophylaxis protocol, analyze the epidemiological profile of accidents and develop strategic actions for the prevention and control of the disease based on evidence. To minimize the limitations of this study, duplicates and incomplete and inconsistent records were identified, with methodological rigor in the statistical analyses.

Therefore, it is important to highlight the need for health teams to receive regular updates on the epidemiology of the disease, prevention methods and immunization protocols, as well as on the correct completion of the reporting form, which is considered extremely important for monitoring diseases and health problems. Finally, it is also recommended that qualitative studies be developed to assess professionals' and managers' perception regarding reporting, care flows and prophylaxis, in addition to the implementation of health education actions that promote awareness among the population about the risks associated with disease transmission, especially in the wild cycle.

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AUTHORS' CONTRIBUTIONS

Laysa Lindaura Lau Rocha Cordeiro contributed to project administration, literature search, formal analysis, conceptualization, methodology, data curation, statistics, writing (first draft, review, and editing), investigation, resources, software, supervision, validation, conclusions. **Maria Olívia Soares Rodrigues** and **Louisiana Regadas de Macedo Quinino** contributed to writing (review and editing), interpretation of results, conclusions, validation, and visualization. **Francisco Duarte Farias Bezerra** contributed to project administration, methodology, interpretation of results, and review. **Raylene Medeiros Ferreira Costa** contributed to data curation, software, interpretation of results, and review. **Emília Carolle Azevedo de Oliveira** contributed to project administration, literature search, formal analysis, writing (review and editing), investigation, methodology, resources, supervision, validation, and conclusions.

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

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Hospital Santa Cruz

ORIGINAL ARTICLE

Microbiological control of adapted liquid dosage forms in a pediatric hospital from Manaus

Controle microbiológico de formas farmacêuticas líquidas adaptadas em um hospital pediátrico de Manaus

Control microbiológico de formas farmacéuticas líquidas adaptadas en un hospital pediátrico de Manaus

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Corresponding Author:
Karen Regina Carim da Costa Magalhães
krccosta@ufam.edu.br

Address: Avenida General Rodrigo Octávio, 6200, Setor Sul, Faculdade de Ciências Farmacêuticas. Manaus - AM. Brazil. CEP: 69080-900

Felipe Mota Tashiro[1];
Adriana da Silva Carvalho[2];
Igor Rafael dos Santos Magalhães[2];
Karen Regina Carim da Costa Magalhães[2];

[1] *Universidade Estadual Paulista "Júlio de Mesquita Filho" – Campus Araraquara, Araraquara, SP, Brazil.*
[2] *Faculdade de Ciências Farmacêuticas - Universidade Federal do Amazonas, Manaus, AM, Brazil.*

ABSTRACT

Background and Objectives: Ideal dosage forms for pediatric use are liquid because this population has difficulty swallowing. However, the pharmaceutical market does not have a large arsenal. To solve this situation, it is necessary to adapt drugs intended for the adult public in the form of oral solutions that allow the use of pediatric patients. Such practice changes the physicochemical and microbiological properties of these drugs. Most studies on pharmaceutical adaptations are directed to the physicochemical stability. Therefore, this study aimed to perform microbiological control of liquid pharmaceutical forms adapted in a pediatric hospital. **Methods:** Microbiological analysis was performed according to the specifications of the Brazilian Pharmacopoeia for non-sterile products. The total number of mesophilic microorganisms and the presence of pathogenic microorganisms were counted. **Results:** During the study period, 36 pharmaceutical adaptations were prepared in the hospital and then, after applying exclusion criteria, 16 samples were selected for microbiological analysis. The most common classes were diuretics, antihypertensives and psycholeptics. No preservatives were used in the preparation of the analyzed pharmaceutical adaptations. Half of the adaptations had a total number of mesophilic microorganisms above the allowed limit on the day of manipulation, 43.75% in the middle of the shelf life and 62.5% in the end of the shelf life. **Conclusion:** Only 03 (18.75%) adaptations were within the acceptable microbial limits established throughout the study. Regarding the presence of pathogens, all were free from the pathogens Escherichia coli, Salmonella sp., Pseudomonas aeruginosa and Staphylococcus aureus during the study period**.**

Keywords: *Brazilian Pharmacopeia. Pediatric Hospitals. Pharmaceutical Preparations.*

RESUMO

Justificativa e Objetivos: Formas farmacêuticas líquidas são ideais para pacientes pediátricos, uma vez que esta população apresenta dificuldades de deglutição. Entretanto, o mercado farmacêutico não dispõe de um grande arsenal terapêutico. Para contornar esta situação, é necessária a adaptação de medicamentos voltados ao público adulto para a forma de soluções orais, que permitem o emprego em pacientes pediátricos. Todavia, esta pode alterar as propriedades físico-químicas e microbiológicas destes fármacos. De acordo com a literatura, grande parte dos estudos com adaptações farmacêuticas são direcionados a estabilidade físico-química, e os parâmetros microbiológicos são menos avaliados. Portanto, o objetivo deste trabalho foi realizar o controle microbiológico das formas farmacêuticas líquidas adaptadas em um hospital pediátrico. **Métodos:** A análise microbiológica foi realizada conforme especificações da Farmacopeia Brasileira para produtos não estéreis. Realizou-se os testes de contagem do número total de microrganismos mesófilos e da presença de microrganismos patogênicos. **Resultados:** No período do estudo, 16 amostras foram selecionadas para análise microbiológica. Dentre os medicamentos as classes mais frequentes foram diuréticos, anti-hipertensivos e psicolépticos. Não foram utilizados conservantes no preparo das adaptações farmacêuticas analisadas. Metade das adaptações apresentaram contagem do número total de microrganismos mesófilos acima do limite permitido no dia da manipulação, 43,75% na metade do período de validade e 62,5% no prazo de validade. **Conclusão:** Apenas 03 (18,75%) adaptações estavam dentro dos limites microbianos aceitáveis estabelecidos durante todo o estudo. Com relação a presença de patógenos, todas foram isentas dos patógenos *Escherichia coli*, *Salmonella sp.*, *Pseudomonas aeruginosa* e *Staphylococcus aureus* no período do estudo.

Descritores: *Farmacopeia Brasileira. Hospitais Pediátricos. Preparações Farmacêuticas.*

RESUMEN

Justificación y Objetivos: Las formas farmacéuticas líquidas son ideales para pacientes pediátricos, ya que esta población presenta dificultades para deglutir. Sin embargo, el mercado farmacéutico no dispone de un amplío arsenal terapéutico. Para superar esta situación, es necesaria la adaptación de medicamentos destinados al público adulto a la forma de soluciones orales, que permitan su uso en pacientes pediátricos. No obstante, esto puede alterar las propiedades físico-químicas y microbiológicas de estos fármacos. De acuerdo con la literatura, gran parte de los estudios sobre adaptaciones farmacéuticas están dirigidos a la estabilidad físico-química, y los parámetros microbiológicos son menos evaluados. Por lo tanto, el objetivo de este estudio fue realizar el control microbiológico de las formas farmacéuticas líquidas adaptadas en un hospital pediátrico. **Métodos:** El análisis microbiológico se realizó conforme a las especificaciones de la Farmacopea Brasileña para productos no estériles. Se realizaron pruebas de recuentos del número total de microorganismos mesófilos y de la presencia de microorganismos patógenos. **Resultados:** Durante el período del estudio, se seleccionaron 16 muestras para el análisis microbiológico. Entre los medicamentos, las clases más frecuentes fueron: diuréticos, antihipertensivos y psicolépticos. No se utilizaron conservantes en la preparación de las adaptaciones farmacéuticas analizadas. La mitad de las adaptaciones presentaron un recuento del número total de microorganismos mesófilos por encima del límite permitido el día de la manipulación, el 43,75% en la mitad del período de validez y el 62,5% en el período de validez. **Conclusión:** Solo 03 (18,75%) adaptaciones estaban dentro de los límites microbianos aceptables establecidos a lo largo del estudio. En cuanto a la presencia de patógenos, todos extensas de los patógenos *Escherichia coli, Salmonella sp., Pseudomonas aeruginosa* y *Staphylococcus aureus* durante el período de estudio.

Palabras Clave: *Farmacopea Brasileña. Hospitales Pediátricos. Preparaciones Farmacéuticas.*

INTRODUCTION

In the case of active substances, liquid pharmaceutical forms are ideal for use in the pediatric population, as they are easily swallowed and allow greater control over the dose administered. Such adjustments are essential, since pediatric patients have pharmacokinetic and pharmacodynamic differences that vary rapidly throughout childhood, and are more exposed to drug-related adverse effects.[1-4]

Although ideal, there is a notable absence of drugs in liquid pharmaceutical form in pediatric clinical practice, due to legal, ethical and economic issues, where this section of the population is generally not included in clinical trials for the development of new drugs, or due to the fact that some drugs have poor bioavailability or effectiveness when prepared in aqueous solution.[5,6]

In this context, a common practice in many children's hospitals is the adaptation of pharmaceutical forms for administration to children, particularly inpatients. These adapted formulations can be obtained by different methods, from crushing a tablet or opening a capsule to use its contents. The resulting powder can be dissolved or suspended in various excipients to produce a liquid consistency medicine for oral use, or put back into smaller capsules or sachets.[3,7]

The act of reformulating medicines into an oral extemporaneous preparation for prescription outside the approved

indications (age range, dosage, presentation) or for use by a route of administration other than that originally developed is defined in science as unlicensed or *off-label* use.[8]

Although the overall burden of inefficient and unsafe pharmacotherapy in children has never been established, the high use of *off-label* medicines is worrying.[6] The prevalence of prescriptions with adapted pediatric medicines is estimated at 3.2% to 95%; where, 26% to 95% in neonates, 2.7% to 51.2% in outpatients and 9.0% to 79.0% in inpatients. Developing countries are the most severely affected, as people aged between 0 and 18 make up a large proportion of the population and are the most vulnerable to disease.[3]

It can be seen that adapted medicines are a solution not only for personalizing therapy in paediatric patients, but also for specific therapies when there are no commercial alternatives available. However, splitting the tablet, crushing and/or dissolving it to obtain a liquid pharmaceutical form offers different risks to the patient since there is not enough safety information on drug interactions, stability or efficacy caused by potential changes in bioavailability.[3,9]

Environmental factors can affect the physicochemical and microbiological stability of these drugs, such as temperature, light, humidity, radiation, air, particle size, solvents, pH and the presence of contamination or the intentional mixing of different products, as well as the hygiene and sterility of the place where they will be handled.[10]

In the literature, most of the quality control work on pharmaceutical adaptations in hospitals focuses on analyzing the physicochemical stability of the formulations. However, it is important to emphasize the need to assess the load of 'non-compliant microorganisms' in these products, which can cause organoleptic changes and interfere in the drug's degradation process, leading to a reduction in its efficacy and safety. In addition, the high microbial load can cause serious infections in these populations.[12]

Pharmaceutical professionals must consider microbial contamination and materials that pose a danger to patients, especially vulnerable groups such as pediatric patients. The addition of preservatives and good handling practice measures are crucial in controlling mold, inhibiting yeast growth and protecting against bacterial spread.[13,14]

In view of this, the research justifies its raison d'être in the need to carry out microbiological control of these extemporaneous formulations in a hospital in order to contribute to improving the handling process, reducing the risk of contamination of patients or even accelerated degradation of the medicines produced and, finally, to generate sufficient data available on the microbiological control of these adaptations,[11,15] since no studies on the subject were found in the city, although the use of adapted products has already been investigated in the city of Manaus.[16,17]

Therefore, the aim of this study was to carry out microbiological control of adapted liquid pharmaceutical forms in a pediatric hospital, following the specifications of the Brazilian Pharmacopoeia for non-sterile products, using the most probable number for mesophilic microorganisms and testing for the pathogenic bacteria *Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus* and *Salmonella* sp.

METHODS

Study design - A prospective study was carried out on the microbiological control of liquid pharmaceutical forms adapted in the pediatric hospital pharmacy, with collections from September 2017 to May 2018.

Survey and selection of adapted pharmaceutical forms – Initially, a survey was carried out of all the formulations adapted in the hospital pharmacy during the study period, and the total number of formulations produced was obtained. These formulations were then evaluated in terms of their composition and classified according to their pharmacological classes, determined using the ATC (Anatomical Therapeutic Chemical) methodology.[18] After this process, exclusion criteria were applied to select which formulations would be evaluated microbiologically, including: being an antimicrobial agent, not being for oral use, a shelf life of less than 7 days and production in insufficient quantities for the study's analysis.

Together with the formulations selected for microbiological analysis, an aliquot of the excipients simple syrups and carboxymethylcellulose used in the preparation of the pharmaceutical adaptations were inserted, both of which have a shelf life of 180 days and are prepared in the hospital pharmacy itself.

After selecting the medicines and excipients used in the liquid formulations, the samples obtained for analysis were grouped according to the shelf life established by the site's standard operating procedure: Group 1 (7 to 20 days), Group 2 (30 days), Group 3 (35-48 days), Group 4 (60 days), Group 5 (90 days) and Group 6 (180 days).

For the microbiological analysis, 03 units were requested from the same batch of each selected sample, which were collected at "time zero", i.e. on the day of handling. These were then transported in a refrigerated box to the laboratory and kept under refrigeration (4 °C) until the moment of analysis.

Microbiological analysis – Microbiological analyses were carried out immediately after preparing the formulations (time zero), halfway through the shelf life and when the shelf life was reached, using previously prepared culture media incubated in an oven at 32 ºC ± 2.5 ºC for 24 hours to assess sterility after preparation and sterilization in an autoclave. Tests were carried out for the total count of mesophilic microorganisms and for pathogens, in accordance with the criteria for non-sterile pharmaceutical products as specified in the Brazilian Pharmacopoeia 5th edition.[19]

Counting the total number of mesophilic microorganisms by most probable number

- Mesophiles were analyzed using the most probable number method, which consists of evaluating the growth of viable microorganisms within 5 days, in Casein-Soy broth (KASVI, São José dos Pinhais-PR) incubated in an oven at 32 ºC ± 2.5 ºC. The analysis was carried out by preparing dilutions, in triplicate, at a ratio

of 1:10; 1:100 and 1:1000 of the formulations analyzed. Positive and negative tubes were recorded and compared according to the specifications in the Brazilian Pharmacopoeia, where the limit for total aerobic bacteria count (UFC/g or mL) is 200 UFC/g or mL of product. The result obtained is expressed as Most Probable Number per gram or milliliter of product, MPN per g or MPN per mL of product.

Testing for *Escherichia coli*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* - The tests for *E. coli, P. aeruginosa and S. aureus* were initially carried out together, as the sample preparation and pre-incubation stages followed the same procedure. To prepare the sample, 1 mL of the formulation was inoculated into a tube containing 9 mL of Casein-Soy broth. The contents of this tube were transferred to a flask containing 90 mL of Casein-Soy broth (pre-incubation stage) and incubated for 18-24 hours at 32 ºC ± 2.5 ºC. After this period, the plates were sown on Cetrimide agar (HiMEDIA, Mumbai, Maharashtra, India) to test for Pseudomonas sp. and sown on Salted Mannitol agar (HiMEDIA, Mumbai, Maharashtra, India) to test for Staphylococcus sp. The plates were incubated in an oven for 18-24 hours at 32 ºC ± 2.5 ºC and colony growth was observed. For Escherichia coli, an aliquot of 1 mL of the pre-incubation medium was transferred to an erlenmeyer flask containing 100 mL of MacConkey broth (enrichment) (KASVI, São José dos Pinhais-PR), which was incubated for 18-24 hours at 43 ºC ± 1 ºC and then sown on a plate (subculture) containing MacConkey agar (HiMEDIA, Mumbai, Maharashtra, India), and incubated for 18-72 hours at 32 ºC ± 2.5 ºC.

The results obtained, following the limits determined by the Brazilian Pharmacopoeia, after the tests, should be negative, i.e. the absence of these pathogens, in the samples of the products analyzed.

Search for *Salmonella sp.* - For the sample preparation and pre-incubation period, 10 mL of sample was added to a flask containing 90 mL of Casein-Soy broth, which was then incubated for 18-24 hours at 32 ºC ± 2.5 ºC. After incubation, a 0.1 mL aliquot of the solution containing the sample was inoculated into a tube containing 10 mL of Selenite-Cystine broth (HiMEDIA, Mumbai, Maharashtra, India). It was incubated for 18-24 hours at 32 ºC ± 2.5 ºC. A loop of the Selenite-Cystine broth was removed using a bacteriological loop and sown on a plate containing Xylose Lysine Deoxycholate - XLD agar (Biokar Diagnost, Beauvais Cedex France), which was incubated for 18-72 hours at 32 ºC ± 2.5 ºC.

The results obtained, following the limits determined by the Brazilian Pharmacopoeia, after the tests, is the absence of this pathogen in the samples of the products analyzed.

Ethical aspects – This project was carried out without the need for approval by the Research Ethics Committee. However, a consent form was previously issued by the Health Unit's Board of Directors for the use of the formulations employed in the study.

RESULTS

Survey and selection of pharmaceutical adaptations– Data was collected from the register of formulations produced in 2017. During this period, 36 pharmaceutical adaptations were prepared. Half of them (50%) were antihypertensives, antibacterials, psycholeptics and diuretics, in the proportion of 11.1% each respectively, and antiepileptics (5.6%), according to the ATC (Anatomical Therapeutic Chemical) methodology.[18] The other half was distributed among other ATC classes. In view of this data, the exclusion criteria were applied, as shown in Table 1.

Among the exclusion criteria applied, 14 (41.6%) of the excluded adaptations did not meet the criterion of sufficient quantity for the study. As an example, we can mention the antiepileptic drug topiramate, which had its adaptation suspended because the tablets were out of date and would be taken for disposal. This was followed

Table 1. Number of pharmaceutical adaptations excluded from the study after applying the exclusion criteria (N=22).

Exclusion criteria	Number of adaptations included (%)
Contains antimicrobial agent in its formulation	6 (16,6%)
Not for oral use	1 (3%)
Expiration date less than 7 days	0 (0%)
Insufficient quantity for study	15 (41,6%)

Table 2. Pharmaceutical adaptations selected for the study (N=14).

Group	Adapted drug	ATC classification	Expiration date
01	Clobazam	psycholeptic	15 days
01	Sildenafil	urological	20 days
02	Spiranolactone	diuretic	30 days
02	Losartan	antihypertensive renin angiotensin antagonist	30 days
02	Methadone	other nervous system drugs	30 days
03	Propranolol	beta-blocker	45 days
03	Captopril	antihypertensive renin angiotensin antagonist	45 days
03	Midazolam	psycholeptics	48 days
04	Dexamethasone	corticosteroid	60 days
04	Hydrochlorothiazide	diuretic	60 days
04	Methyldopa	antihypertensive	60 days
05	Furosemide	diuretic	90 days
05	Nifedipine	calcium channel blocker	90 days
06	Potassium Chloride 6%	mineral supplementation	180 days

by the exclusion of 6 (16.6%) adaptations containing antimicrobial agents and 1 (3%) formulation because it was not administered orally. Adapted formulations with a shelf life of less than 7 days were not excluded.

As a result, 14 pharmaceutical adaptations were selected for the study, as shown in Table 2.

The composition of the pharmaceutical adaptations was then analyzed (Table 3). It was found that simple syrup is used as the vehicle and carboxymethylcellulose (CMC) as the viscosifying/dispersing agent. These have a shelf life of 180 days and are prepared in the hospital pharmacy itself, being incorporated into the adapted formulations according to production.

Table 3 shows that in half of the adaptations selected for the study, distilled water was added as a diluent for the drug in the syrup. The use of simple syrup in extemporaneous formulations is a positive factor both for the taste of pediatric patients, as it is able to mask the taste of some drugs, and to promote their greater stability, due to its hypertonic characteristic capable of inhibiting bacterial growth.[20]

In addition, citric acid is an input used to acidify the medium, which can provide stability to the drug or promote its dissolution in the formulation, especially for the adaptation of captopril, being able to act as a stability promoter, as described by. No preservatives or flavor adjuvants are used.

Microbiological analysis - The total count of mesophilic microorganisms, after analysis of the times proposed methodologically, obtained the results that can be seen in Table 4, considering the microbial limits for non-sterile products in the total count of fungi/yeasts of 20 UFC/g or mL and for the total count of aerobic bacteria the limit of 200 UFC/g or mL of product.[19]

Based on the results shown in Table 4, together with the limits determined in the literature, of the 16 samples analyzed at time zero, 8 (50.0%) showed non-compliant results. Among these, clobazam, methadone, propranolol and dexamethasone did not comply with the limits stipulated for fungi/yeasts, while spironolactone, hydrochlorothiazide, methyldopa and carboxymethylcellulose did not meet the limits for aerobic bacteria.

In the half-life analysis of the formulations, 7 (43.75%) showed non-compliant results, with clobazam, spironolactone methadone, propranolol and captopril being outside the stipulated limits for fungi/yeasts and dexamethasone and methyldopa being outside the limits for aerobic bacteria.

In the analyses referring to the final deadline, 10 (62.5%) of the formulations did not comply with the established parameters. Spironolactone, methadone, propranolol and dexamethasone were found to be outside the permitted limit of CFU/g or mL of product and the samples of clobazam, sildenafil, hydrochlorothiazide, methyldopa and furosemide failed to meet the permitted limit for aerobic bacteria.

These data show that a large proportion of the formulations submitted for analysis, during the period of the deadline, do not comply with the microbiological

Table 3. Excipients used in adapted formulations (N=14).

Excipient	Function	Use in formulations (%)
Distilled/purified water	Thinner	7 (50%)
Syrup	Viscosifier/dispersant	13 (92,8%)
Carboxymethylcellulose	Viscosifier/dispersant	5 (35,7%)
Citric acid	pH adjustment/preservative	6 (42,8%)

Table 4. Total count of mesophilic microorganisms in Most Probable Number (MPN) per g or mL of product (N=16).

	Result mesophile count in MPN per g or mL of product		
Drug/ Excipient	**Zero time**	**½ life**	**Expiration date**
Clobazam	27*	64*	>1100*
Sildenafil	15	11	>1100*
Spiranolactone	1100*	75*	43*
Losartan	20	6,1	>1100*
Methadone	95*	23*	160*
Propranolol	95*	38*	150*
Captopril	9,3	29*	11
Midazolam	19	16	11
Dexamethasone	28*	1100*	35*
Hydrochlorothiazide	290*	15	460*
Methyldopa	290*	>1100*	290*
Furosemide	-	-	>1100*
Nifedipine	15	-	6
Potassium Chloride 6%	6,1	6,1	3
Simple syrup	-	-	3
Carboxymethylcellulose	>1100*	14	-

**Above the permitted microbial limit, non-sterile products have a total fungal/yeast count of 20 CFU/g or mL and a total aerobic bacteria count of 200 CFU/g or mL. MPN= most probable number.*

limits, either in terms of aerobic bacteria or fungi/yeasts. Studies such as the one by Mugoyela (2010), show that the main contaminants of these non-sterile formulations are aerobic bacteria such as *Bacillus spp* and fungi such as *Candida spp* and *Aspergillus spp*.

In the results obtained from the captopril and hydrochlorothiazide formulations, variations were observed between their approval and disapproval, according to the limits stipulated by the pharmacopoeia, during the study period. Possible reasons for this include handling errors, environmental contamination during analysis or even a decline in the cell viability of the microorganism during storage.[21]

The pharmaceutical adaptations that maintained acceptable microbial limits throughout the study period were midazolam, nifedipine and potassium chloride 6%, representing 18.75% of the adapted drug samples. When analyzing the Standard Operating Procedure (SOP) for these adaptations, we found that the adaptation was carried out using sterile medication (ampoules), except in the case of nifedipine, which was made using slow-release tablets.

All the pharmaceutical adaptations complied with the legal requirement for the absence of the following pathogens: *Escherichia coli, Salmonella sp., Pseudomonas aeruginosa* and *Staphylococcus aureus*.

DISCUSSION

During the survey and classification of formulations that could be adapted in the pharmacy sector of the hospital where the study took place, it was found that the main pharmacological classes subjected to this process during the study period were: antihypertensives, antibacterials, psycholytics and diuretics. Other studies, such as the one by García-López (2020), using the same ATC classification, show that the main classes of *off-label* drugs are those for the central nervous system, gastrointestinal tract and respiratory system. The prescription profile is different to that of the hospital under study, except for psycholytics, which are classified as drugs that act on the central nervous system.

With regard to the composition of the formulations, it can be seen that no preservatives were used, which can largely contribute to the microbiological growth observed in the results obtained from the mesophilic microorganism count, where 13 (81.25%) samples showed a total number of mesophilic microorganisms above the permitted limits for fungi/yeasts or aerobic bacteria.[17]

Microbial contamination above the permitted limits can easily compromise the health of pediatric patients, because in some cases the presence of microorganisms alone is not harmful to health, but the toxins they produce can trigger symptoms such as diarrhea, acute gastroenteritis, stomach pain or even, in severe cases, death.[23]

Only 3 (18.75%) formulations were found to be within acceptable microbial limits during analysis: midazolam, nifedipine and potassium chloride 6%. These results show the need for training and adequate infrastructure for the manufacture of these products so that patient safety can be ensured.[8,21]

When it came to testing for pathogens, all the pharmaceutical adaptations were free of *Escherichia coli, Salmonella sp., Pseudomonas aeruginosa* and *Staphylococcus aureus*, thus within the limits recommended by the pharmacopoeia. It is therefore interesting to understand that in the case of testing for *S. aureus*, when not producing enterotoxins, and *E. coli* are important markers for assessing the hygiene of the hands of the handler and the workbench during the process.[24,25]

Pseudomonas aeruginosa is described as an important human pathogen, it has the ability to contaminate non-sterile products due to its versatility to grow in unfavorable environments and its intrinsic and acquired resistance to antimicrobials, its absence in the analysis is a good marker in monitoring the quality of water and food, as well as the absence of Salmonella sp., being especially dangerous for children and immunocompromised, and can lead to fatal dehydration.[26,27]

The scarcity of commercial formulations suitable for the pediatric public, considering differences in physiological and metabolic response, makes it necessary to use *off-label* preparations. Therefore, in order to ensure their quality, rigorous safety assessment is necessary, considering the possibility of adverse reactions, toxicity and especially physicochemical and microbiological stability.

Therefore, effective microbiological quality control is essential to increase the safety of manipulated medicines, guiding pharmacists to improve their practices through appropriate procedures and access to crucial information on the stability, compatibility, bioavailability and safety of these products

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AUTHOR CONTRIBUTIONS

Felipe Mota Tashiro, **Adriana da Silva Carvalho, Igor Rafael dos Santos Magalhães** e **Karen Regina Carim da Costa Magalhães** contributed to the bibliographical research, writing the abstract, introduction, methodology, discussion, interpretation and description of the results, preparation of tables, conclusions and statistics.

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

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Revista de Epidemiologia e Controle de Infecção

Hospital Santa Cruz

ORIGINAL ARTICLE

Epidemiological profile of patients hospitalized for COVID-19 and diagnosed with ventilator-associated pneumonia

Perfil epidemiológico de pacientes internados por COVID-19 e diagnosticados com pneumonia associada à ventilação mecânica

Perfil epidemiológico de pacientes hospitalizados por COVID-19 y diagnosticados con neumonía asociada al ventilador

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Corresponding Author:
Raphaela de Matos Borges
raphaelamatosb@gmail.com

Address: Rua Sarmento Leite, 245 - Centro Histórico, Porto Alegre, Rio Grande do Sul, Brazil.

Raphaela de Matos Borges[1];
Rute Merlo Somensi[2];
Ariane Baptista Monteiro[3];
Rita Catalina Aquino Caregnato[4];

[1] *Universidade Federal de Ciências da Saúde de Porto Alegre, Porto Alegre, RS, Brazil.*
[2] *Irmandade Santa Casa de Misericórdia de Porto Alegre, Porto Alegre, RS, Brazil.*
[3] *Hospital São Lucas da Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre, RS, Brazil.*
[4] *Universidade Federal de Ciências da Saúde de Porto Alegre, Porto Alegre, RS, Brazil.*

ABSTRACT

Background and Objectives: due to complications associated with Coronavirus Disease-2019 (COVID-19) infection, there was an increase in hospitalizations in intensive care and the use of mechanical ventilation and health-care-associated infections during the pandemic period. Therefore, the objective was to understand the epidemiological profile of patients hospitalized for COVID-19 in an Intensive Care Unit (ICU) who developed ventilation-associated pneumonia (VAP). **Methods:** a retrospective cross-sectional study, with data collection from electronic medical records. It was conducted in a specific ICU for COVID-19, located in southern Brazil, between July 2020 and June 2021. Patients with COVID-19 who developed VAP were included. Patients who developed clinical VAP or who did not have all information available for access were excluded. **Results:** fifty-four patients participated in the study, predominantly male (55.6%), aged 60 years or over (38.9%) and overweight (53.7%). The most prevalent comorbidities were hypertension (63.8%) and diabetes mellitus (20.4%). Only cases of bacterial etiology were identified, with a predominance of the gram-negative *Acinetobacter baumannii* (57.4%), *Pseudomonas aeruginosa* (24.1%), *Klebsiella pneumoniae* (20.4%) and microbial resistance. The predominant clinical outcome was death. **Conclusion:** a similar pattern to that found in the literature regarding the profile of patients admitted to intensive care for COVID-19 who developed VAP was evident. Factors such as immunosuppression, advanced age, and chronic diseases were predominant in the cases. Consistent with the literature, bacterial etiology appears to be more prevalent in VAP as well as the prevalence of gram-negative bacteria and antimicrobial resistance.

Keywords: *COVID-19. Intensive Care Units. Ventilator-Associated Pneumonia. Epidemiological Monitoring.*

RESUMO

Justificativa e Objetivos: devido às complicações associadas à infecção pela doença do Coronavírus-2019 (COVID-19), houve um aumento de hospitalizações em terapia intensiva e do uso de ventilação mecânica e das infecções relacionadas à assistência à saúde no período pandêmico. Diante disso, objetivou-se conhecer o perfil epidemiológico de pacientes internados por COVID-19 em uma Unidade de Terapia Intensiva (UTI) que desenvolveram pneumonia associada à ventilação mecânica (PAV). **Métodos:** estudo transversal retrospectivo, com coleta de dados do prontuário eletrônico. Realizado em uma UTI específica para COVID-19, localizada no sul do Brasil, entre julho de 2020 e junho de 2021. Incluíram-se pacientes com COVID-19 que desenvolveram PAV. Excluíram-se aqueles que desenvolveram PAV clínica ou que não apresentavam informações disponíveis para acesso. **Resultados:** participaram do estudo 54 pacientes, com predominância do sexo masculino (55,6%), faixa etária de 60 anos ou mais (38,9%) e sobrepeso (53,7%). As comorbidades mais prevalentes foram hipertensão arterial sistêmica (63,8%) e diabetes mellitus (20,4%). Identificaram-se somente casos de etiologia bacteriana, com predominância das gram-negativas *Acinetobacter baumannii* (57,4%), *Pseudomonas aeruginosa* (24,1%), *Klebsiella pneumoniae* (20,4%) e de resistência microbiana. O desfecho clínico predominante foi óbito. **Conclusão:** evidenciou-se um padrão semelhante ao encontrado na literatura relacionado ao perfil de pacientes que internaram em terapia intensiva por COVID-19 e que desenvolveram PAV. Fatores como imunossupressão, idade avançada e doenças crônicas apresentaram predominância nos casos. Condizentemente à literatura, a etiologia bacteriana mostrou-se mais prevalente em PAV, assim como a prevalência de bactérias gram-negativas e com resistência a antimicrobianos.

Descritores*: COVID-19. Unidade de Terapia Intensiva. Pneumonia Associada à Ventilação Mecânica. Monitoramento Epidemiológico.*

RESUMEN

Justificación y Objetivos: debido a las complicaciones asociadas a la infección por la enfermedad del Coronavirus-2019 (COVID-19), hubo un aumento en las hospitalizaciones en cuidados intensivos y el uso de ventilación mecánica y las infecciones relacionadas con la atención médica durante el período de pandemia. Por tanto, el objetivo fue comprender el perfil epidemiológico de los pacientes hospitalizados por COVID-19 en una Unidad de Cuidados Intensivos (UCI) que desarrollaron neumonía asociada al ventilador (NAV). **Métodos:** estudio transversal retrospectivo, recogiendo datos de historias clínicas electrónicas. Fue realizado en una UCI específica para COVID-19, ubicada en el sur de Brasil, entre julio de 2020 y junio de 2021. Se incluyeron pacientes con COVID-19 que desarrollaron NAV. Se excluyeron aquellos que desarrollaron NAV clínica o que no tenían información disponible para el acceso. **Resultados:** participaron del estudio 54 pacientes, predominantemente del sexo masculino (55,6%), con edad igual o superior a 60 años (38,9%) y con sobrepeso (53,7%). Las comorbilidades más prevalentes fueron la hipertensión arterial sistémica (63,8%) y la diabetes mellitus (20,4%). Sólo se identificaron casos de etiología bacteriana, con predominio de los gramnegativos *Acinetobacter baumannii* (57,4%), *Pseudomonas aeruginosa* (24,1%), *Klebsiella pneumoniae* (20,4%) y resistencia microbiana. El resultado clínico predominante fue la muerte. **Conclusión:** se evidenció un patrón similar al encontrado en la literatura relacionado con el perfil de los pacientes participantes de la muestra. En los casos predominaron factores como la inmunosupresión, la edad avanzada y las enfermedades crónicas. De acuerdo con la literatura, la etiología bacteriana demostró ser más prevalente en la NAV, así como la prevalencia de bacterias gramnegativas y con resistencia a los antimicrobianos.Parte superior do formulárioParte inferior do formulário

Palabras Clave: *COVID-19. Unidades de Cuidados Intensivos. Neumonía Asociada al Ventilador. Monitoreo Epidemiológico.*

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is transmitted through aerosols and droplets and can cause respiratory symptoms of varying severity. Since the beginning of 2020, when the COVID-19 pandemic was declared by the World Health Organization (WHO), several variants of the new coronavirus have been identified, with different transmission and mortality potentials. Moreover, there have been considerable numbers of cases and deaths worldwide.[1-2] After three years of pandemic, on May 5, 2023, the WHO declared the end of the Public Health Emergency of International Concern associated with COVID-19, due to the downward trend in deaths associated with the disease.[3]

Symptoms caused by coronavirus infection may require hospitalization and, in some cases, intensive care.[4] During the peaks caused by COVID-19, there was evidence of saturation of the Brazilian healthcare system associated with an increase in hospital admissions as well as Intensive Care Unit (ICU) beds.[5]

Healthcare-associated infections (HAIs) are directly associated with intensive care, due to the greater propensity of critically ill patients to develop them. During the COVID-19 pandemic, an increase in HAI rates was

observed.[6] The occurrence of these infections causes numerous complications for patients, such as prolonged recovery time and, consequently, hospital stay, in addition to worsening clinical condition and death.[6-7] In intensive care, ventilator-associated pneumonia (VAP) is the most common nosocomial infection. It is associated with the use of invasive ventilatory support and is characterized when patients present pneumonia after the use of this device from the second day of intubation.[6-7] VAP has a considerable mortality rate, with more than 30% of patients dying.[7]

VAP and COVID-19 became mandatory notification conditions for the Brazilian healthcare system in 2017 and 2022, respectively.[7-8] Epidemiological notification to regional and federal agencies of diseases, such as highly transmissible respiratory infections and nosocomial infections, is of utmost importance to identify rates, patterns and outbreaks, enabling the creation of prevention and control measures.

Given the pandemic scenario that occurred between 2020 and 2023, associated with the increase in ICU admissions and HAIs, the research question was developed: what is the epidemiological profile of patients hospitalized for COVID-19 in an ICU located in Porto Alegre, RS, who developed VAP? Based on this question, the objective was to understand the epidemiological profile of patients hospitalized for COVID-19 in an ICU who developed VAP.

METHOD

This is a retrospective cross-sectional study. This study design is indicated to assess the frequency of variables that are the objects of research investigation.[9]

The sample participants were selected intentionally and non-probably. Those admitted to an ICU in a hospital complex located in Porto Alegre, RS, which exclusively treated adult patients with COVID-19 between July 2020 and June 2021, were included.

Patients admitted to the ICU due to complications from COVID-19 and who received a microbiological diagnosis of VAP were included. Patients with a clinical diagnosis of VAP, i.e., without microbial proof, and those who did not present all the information regarding the variables collected in their medical records were excluded.

Data were collected through research in electronic medical records in the institution's management system, with the researcher's own access, and tabulated in a spreadsheet using Microsoft Excel®. The variables collected were: sex; date of birth and age at the time of admission to the ICU (in years); weight (in kilograms), height (in meters) and Body Mass Index (BMI); presence of comorbidities, such as smoking, diabetes mellitus (DM), hypertension (HT) and history or current condition of malignant neoplasia, heart, kidney, liver, lung and/or immunosuppressive disease; outcome (hospital discharge or death); length of hospital stay (days); length of ICU stay (days); readmission to the ICU after 30 days of transfer to the inpatient unit or discharge; time of invasive mechanical ventilation (IMV) (days); microorganisms identified in the sample; and whether they have microbial resistance to the main antimicrobials used in each case.

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS®). Data were presented as frequencies and percentages. Quantitative variables were expressed as mean and standard deviation when symmetrical, and median and interquartile range when asymmetrical. Variables were compared using the Mann-Whitney test, with statistical significance if p-value was less than 0.05.

This study is part of a larger project entitled "*Inteligência Artificial na Sistematização da Assistência de Enfermagem em pacientes com Síndrome Respiratória Aguda Grave*", which was approved by the Research Ethics Committee (REC) of the institution in question, via Opinion 4.694.150 and Certificate of Presentation of Ethical Consideration (*Certificado de Apresentação para Apreciação Ética*) 45203121.6.0000.5335. The researchers were included in the REC's consolidated opinion through Opinion Amendment 5.329.313. Due to the retrospective nature of the methodology, the application of an Informed Consent Form was not necessary. Therefore, a Commitment Form for Data Use was applied, signed by the researcher. The research was conducted in compliance with the ethical standards required by Resolutions 466/2012, 510/20216 and 580/2018 of the Brazilian National Health Council.

RESULTS

Regarding the sample profile, the majority were male, with a minimum age of 30 and a maximum of 89 years, with a mean of 58.8±14.5 years. The table below presents the relationship of sociodemographic characteristics, age groups and classification according to BMI of the sample.

Table 1. Relationship between sex, age groups and Body Mass Index classifications of patients hospitalized due to complications of COVID-19 and who acquired ventilator-associated pneumonia. Porto Alegre, Rio Grande do Sul, Brazil, 2020-2021.

Variables	N (%)
Male	30 (55.6)
Age group	
30 to 39 years	7 (13.0)
40 to 49 years	9 (16.7)
50 to 59 years	6 (11.1)
60 to 69 years	21 (38.9)
70 to 79 years	7 (13.0)
80 years and older	4 (7.4)
Body Mass Index	
Malnutrition	2 (3.7)
Eutrophy	12 (22.2)
Overweight	29 (53.7)
Obesity	11 (20.4)

BMI values ranged from 21.1 to 44.5 points, with a mean of 30.2±5.7. Among the patients with obesity, five (9.3%) had grade I obesity, four had grade II obesity (7.4%) and two (3.7%) had grade III obesity.

Most patients had some comorbidity or risk factor (n=47, 87.0%). History of smoking or active smoking, obesity, hypertension, DM, previous or active diagnosis of malignant neoplasia and/or presence or history of cardiac, hepatic, immunological, pulmonary and renal diseases were considered as comorbidity or risk factor. Table 2 presents the relationship between comorbidities or risk factors identified in the portion of the sample that presented one or more cases (n=47). It was decided not to present the cases of obesity in this study, as they were already presented in Table 1.

Table 2. Comorbidities or risk factors of patients hospitalized due to complications of COVID-19 and who acquired ventilator-associated pneumonia. Porto Alegre, Rio Grande do Sul, Brazil, 2020-2021.

Variables	N (%)
Hypertension	30 (63.8)
Diabetes mellitus	20 (42.6)
Smoking	
Active	2 (4.3)
Former smoker	3 (6.4)
Heart disease	
Coronary artery disease	4 (8.5)
History of aneurysm	1 (2.1)
History of unspecified cardiac surgery	1 (2.1)
Congestive heart failure	2 (4.3)
Liver disease	
Hepatitis	2 (4.3)
Liver transplant recipient	1 (2.1)
Immune disease	
HIV and/or AIDS	2 (4.3)
Myasthenia gravis	1 (2.1)
Antiphospholipid syndrome	1 (2.1)
Use of immunosuppressive medication	6 (12.8)
Lung disease	
Asthma	5 (10.6)
Chronic obstructive pulmonary disease	1 (2.1)
Cystic fibrosis	1 (2.1)
History of pulmonary tuberculosis	2 (4.3)
Obstructive sleep apnea syndrome	1 (2.1)
Lung transplant recipient	1 (2.1)
Kidney disease	
Chronic kidney disease	2 (4.3)
Prior nephrectomy	1 (2.1)
Kidney transplant recipient	4 (8.5)
Malignant neoplasm	
History of malignant neoplasm	1 (2.1)
Malignant neoplasm at time of admission	4 (8.5)

Note: HIV - Human Immunodeficiency Virus; AIDS - Acquired Immunodeficiency Syndrome.

Seven patients (14.9%) had heart disease, and one (2.1%) had two concomitant diseases (coronary artery disease and history of aneurysm). Liver disease was present in three (6.4%) patients. Conditions associated with the immune system (autoimmune diseases, infectious diseases that affect immunity and/or use of immunosuppressive medication) were present in ten (21.3%) patients, and six of these were using maintenance immunosuppressive therapy to prevent rejection of the transplanted organ, as four were kidney transplant recipients, one was liver transplant recipient and one was lung transplant recipient. Concerning lung disease, ten (21.3%) had a history or current situation of this health condition, and one (2.1%) had two concomitant lung conditions (cystic fibrosis and lung transplant). Kidney conditions were present in seven (14.9%) patients. As for malignant neoplasia, five (10.6%) had a condition already treated or under treatment at the time of hospital admission for COVID-19.

In relation to infections by microorganisms associated with VAP, 36 (66.7%) patients presented infection by a single microorganism; 16 (26.6%) presented infection by two concomitant microorganisms; and two (3.7%) presented infection by three concomitant microorganisms. Table 3 shows the relationship between the microorganisms found in the sample and the microbial resistance of each specimen.

All infections were caused by bacterial pathogens, with *Staphylococcus aureus* being the only gram-positive pathogen. All cases of carbapenem-resistant *Klebsiella pneumoniae* were *K. pneumoniae carbapenemase* (KPC), i.e., carbapenemase enzyme producers. Regarding *S. aureus*, all bacterial isolates showed sensitivity to methicillin/oxacillin.

Table 3. Relationship between microorganisms and microbial resistance rate of causative agents of ventilator-associated pneumonia in patients hospitalized due to complications of COVID-19. Porto Alegre, Rio Grande do Sul, Brazil, 2020-2021.

Microorganism	N (%)
Acinetobacter baumannii	31 (57.4)
Carbapenem-resistant	31 (100*)
Citrobacter koseri	1 (1.9)
Carbapenem-resistant	-
Enterobacter cloacae	1 (1.9)
Carbapenem-resistant	1 (100*)
Enterobacter sp	2 (3.7)
Carbapenem-resistant	-
Klebsiella aerogenes	1 (1.9)
Carbapenem-resistant	1 (100*)
Klebsiella pneumoniae	11 (20.4)
Carbapenemase producers (KPC)	8 (72.7*)
Klebsiella variicola	1 (1.9)
Carbapenem-resistant	1 (100*)
Pseudomonas aeruginosa	13 (24.1)
Carbapenem-resistant	5 (38.5*)
Pseudomonas sp	1 (1.9)
Carbapenem-resistant	-
Serratia marcescens	3 (5.6)
Carbapenem-resistant	2 (66.7*)
Staphylococcus aureus	6 (11.1)
Methicillin/oxacillin-resistant	-
Stenotrophomonas maltophilia	3 (5.6)
Carbapenem-resistant	-

*Notes: - Numerical data equal to zero not resulting from rounding; *Percentage of microbial resistance of the microorganism in question.*

Concerning clinical outcomes, most patients died (n=43, 79.6%). Only one (1.85%) patient was readmitted to the ICU within 30 days after discharge from the first intensive care admission. There was only one (1.9%) case of reintubation within 30 days associated with accidental extubation.

The length of hospital stay had a minimum value of 11 days and a maximum of 104 days, with a median of 33 (22;44). The length of ICU stay ranged from six to 90 days, with a median of 29 (20;41). As for the length of IMV, the data showed a minimum time of six and a maximum of 75 days, with a median of 26 (19;40). From the comparison of these data with the clinical outcomes of discharge or death, the result shown in Table 4 was obtained.

Table 1. Relationship between clinical outcomes and variables of length of hospital stay, length of Intensive Care Unit stay, and duration of invasive mechanical ventilation of patients hospitalized due to complications of COVID-19 who acquired ventilator-associated pneumonia. Porto Alegre, Rio Grande do Sul, Brazil, 2020-2021.

Variable	Death (n=43) Med (Interq)	Discharge (n=11) Med (Interq)	p-value
Length of hospital stay	25 (20;40)	45 (44;74)	<0.001+
Length of ICU stay	22 (17;40)	35 (33;59)	0.002+
Length of IMV	22 (17;38)	32 (27;52)	0.014+

Note: Med - median; Interq - interquartile range; +Mann-Whitney test.

DISCUSSION

The profile of patients admitted to the ICU due to COVID-19 and developed VAP included males, aged between 60 and 69 years, overweight, and preexisting comorbidities, with the majority dying during hospitalization. Accordingly, a review conducted in 2023 showed that advanced age, males, and the presence of preexisting comorbidities were risk factors for worsening COVID-19 infection, consistent with the findings of this study.[10]

The mean age found in the sample was 58.8 years, with more than 50% of patients being 60 years or older. Similarly, an observational study carried out in 2021 showed a mean age of 64 years in patients with COVID-19 who developed VAP.[11] The predominance of patients over 60 years of age may be associated with the immunological vulnerability found in this population, increasing susceptibility to infections and more serious complications.[10-11]

A considerable portion of the sample had a BMI equal to or greater than 30 kg/m^2, which, in the Ministry of Health (MoH) classification for adults (age group composed of people between 18 and 59 years old), is defined as obesity.[12] However, the MoH classification differs for people aged 60 or over, where rates in this range are not classified as obesity, but as overweight.[12] When applying this distinction to the sample, composed mainly of older adults, a predominance of overweight was observed, despite the majority having a BMI equal to or greater than 30 kg/m^2. The literature has identified a relationship between overweight and, especially, obesity, and an increase in severity and mortality in cases of infection by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). A meta-analysis carried out in 2020, based on 16 studies that presented a population with more than 100,000 patients with COVID-19, identified a direct relationship between BMI and the severity and mortality of the infection by the disease.[13] No studies were found that relate excess weight in patients who developed VAP after hospitalization for complications associated with COVID-19. However, from the analysis, it can be inferred that the results found regarding BMI are consistent with those found in the literature, since patients in the sample were admitted to intensive care due to complications associated with the virus infection.

Among the comorbidities observed in the sample, there was a predominance of hypertension and DM, respectively. Hypertension is the most prevalent comorbidity in cases of severe COVID-19, linking the complications associated with SARS-CoV-2 infection to the binding of the virus to angiotensin-converting enzyme (ACE) receptors.[14] A study carried out in 2021 shows that, when using angiotensin-converting enzyme inhibitors (ACEIs), which inhibit the expression of ACE1 and promote the expression of ACE2, there is an excess of this protein in the body, allowing for an increase in susceptibility to coronavirus infection, severity and mortality from the disease.[14] In line with this study, a review carried out in 2022 addresses that hypertension, in isolation, does not present an aggravating factor in cases of COVID-19, and ceasing the use of antihypertensives from the ACE inhibitor class is not a protective factor for complications associated with SARS-CoV-2 infection, recommending maintaining the use of drug therapy in order to also avoid target organ damage associated with uncontrolled hypertension.[15]

Studies have shown an influence on the occurrence of severe cases of COVID-19 in patients with DM. Based on the literature, it can be inferred that hyperglycemia negatively influences the action of the immune system, as well as promoting a state of chronic systemic inflammation, providing greater susceptibility to the severe form of COVID-19. The influence of the binding of SARS-CoV-2 to ACE2 produced by the pancreas in severe cases of the disease in diabetic patients is also highlighted.[16]

During the course of this research, a considerable number of patients who received solid organ transplants prior to hospitalization due to COVID-19 stood out. It is inferred that this result is associated with the use of immunosuppressive medications to maintain the transplant, which causes a reduction in the immune response to antigens, such as the coronavirus. Another study presented data that are in line with the findings of research.[17] A retrospective cohort study evaluating 600 patients who underwent solid organ transplants and were diagnosed with COVID-19 revealed higher rates of hospitalization, ICU admission, and mortality in transplant patients with the disease. Patients infected with SARS-CoV-2 were compared with those who had never received organ

transplants, with a predominantly older adults with other comorbidities standing out in the transplant group.[17] A systematic review that assessed the impact of COVID-19 on patients who received solid organ transplants concluded that mortality was not associated with immunosuppression, but rather with the advanced age of these patients.[18] Therefore, there is a need for new studies to analyze the relationship between mortality from COVID-19 and immunosuppression caused by maintenance medications for late transplants. No evidence was found indicating a relationship between VAP, COVID-19, and solid organ transplant recipients.

Furthermore, the study included four patients who were undergoing oncological treatment during their hospitalization due to complications associated with the coronavirus and who developed pneumonia due to the use of IMV. This data is consistent with that found in a study that assessed the impacts of the pandemic on oncological patients, identifying a higher prevalence of nosocomial infections in these patients, with VAP being the most common in patients with COVID-19.[19] It can be inferred that, similarly to what was previously mentioned in the cases of transplant recipients, patients undergoing cancer treatment are more susceptible to infections and complications associated with them, due to the immunosuppression associated with drug therapy.[19]

Among the comorbidities, the prevalence of patients with lung diseases also stood out, totaling ten cases of history or active disease of these. Accordingly, the study identified that patients diagnosed with diseases such as asthma, chronic obstructive pulmonary disease, obstructive sleep apnea and hypopnea syndrome, emphysema and lung carcinoma presented greater complications associated with COVID-19 when compared to patients infected by the virus, but who did not present any respiratory tract comorbidity.[20] This result is associated with the nature of the disease, since COVID-19 is considered an acute respiratory infection, which can cause, in patients with previous pulmonary comorbidities, an exacerbation of the chronic condition, with worsening of respiratory function and development of serious complications, such as acute respiratory failure and acute respiratory distress syndrome.[10]

In the present study, only pathogens causing VAP of bacterial etiology were identified. Among these, a greater number of infections caused by gram-negative bacteria were observed, with the three main causes of infection being, respectively, *A. baumannii*, *P. aeruginosa* and *K. pneumoniae*. The first presented 100% microbial resistance, which is consistent with what was found in the literature. As presented by the Brazilian National Health Regulatory Agency, an increase in the rates of microbial resistance associated with *A. baumannii* strains was observed.[21] Furthermore, a literature review indicates that more than 20% of nosocomial infections in ICUs are caused by this gram-negative bacterium, which is the main causative agent of VAP, with a considerable increase in cases of infection associated with *A. baumannii* in recent years.[22] According to the findings in the study, *P. aeruginosa* and *K. pneumoniae* were also predominant in the narrative review.[23] As for gram-positive microorganisms, the only one present in the sample was *S. aureus*. A cohort study carried out in 2023 showed that this is the most predominant gram-positive bacteria in pneumonias associated with the use of IMV, as evidenced.[24] No studies were found that presented the survey of VAP associated with one or more causative microorganisms.

The study showed that, regardless of the outcome, the median length of hospital stay was over 30 days. Concerning the length of ICU stay, the median was 29 days. In line with this, another study presented values higher than those found in this study, with a median of 39.5 days of hospital stay and 43 days of ICU stay in cases of patients admitted to the ICU due to complications from COVID-19 and diagnosed with VAP.[24] Due to the unavailability of these data, this study did not analyze the number of days on IMV until the diagnosis of VAP, but rather the total number of days on IMV until patients' outcome. Therefore, no studies were found that analyzed the total number of days on mechanical ventilation of patients with COVID-19 and VAP until the time of hospital discharge or death.

From the analysis of the associations between the variables of length of hospital stay, ICU stay and IMV and clinical outcomes, fewer days were observed in the cases of patients who died during hospitalization compared to those who were discharged from hospital. It is inferred that this result is related to the severity of sample participants, since, due to instability, patients presented worsening of their general condition and death shortly after transfer to the ICU.

Most patients died during hospitalization, due to the predominance of comorbidities, advanced age, and the absence or small number of people vaccinated against COVID-19 during the study period, as well as infection by microorganisms that cause VAP, allowing the occurrence of cases of acute respiratory failure, acute respiratory distress syndrome, sepsis, septic shock, and death. Although vaccination against COVID-19 began in the country during the study period, only a small percentage of Brazilians had received one or more doses of the vaccine, which explains the high mortality rate in the sample as well as due to the multiple comorbidities observed during the research.

Due to the researchers' choice to conduct the study in the ICU of the hospital complex that remained for the longest time with exclusive care for COVID-19 cases, the sample was smaller than expected, which proved to be a limitation of this study. It is suggested that new studies with a larger sample size be carried out. Furthermore, the present study cannot present a comparison of the morbidity and mortality of the disease caused by SARS-CoV-2 before and after the advent of vaccination in the country, due to lack of information in the electronic system, indicating the conduct of studies that present the relationship between the morbidity and mortality linked to COVID-19, before and after the advent of vaccination in Brazil, associated with comorbidities and the multiple pathogens that cause VAP.

It is believed that the results of this research may record part of what occurred during the pandemic and support future research that assesses the relationship between complications associated with SARS-CoV-2 infection, the presence of comorbidities and VAP.

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AUTHORS' CONTRIBUTIONS

Raphaela de Matos Borges contributed to project management, literature search, abstract writing, introduction, methodology, discussion, interpretation and description of results, preparation of tables, conclusions, review and statistics. **Rute Merlo Somensi** contributed to project management, abstract writing, introduction, methodology, discussion, interpretation and description of results, conclusions and review. **Ariane Baptista Monteiro** contributed to abstract writing, introduction, methodology, interpretation and description of results and review. **Rita Catalina Aquino Caregnato** contributed to project management, literature search, abstract writing, introduction, methodology, discussion, interpretation and description of results, conclusions, review and statistics.

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

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ORIGINAL ARTICLE

Comparison of Knowledge, Attitude and Practice (KAP) on visceral leishmaniasis in Rio Grande do Sul

Comparação de Conhecimento, Atitude e Prática (CAP) sobre leishmaniose visceral no Rio Grande do Sul

Comparación de Conocimiento, Actitud y Práctica (CAP) sobre la leishmaniasis visceral en Rio Grande do Sul

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Corresponding Author:
Rovaina Laureano Doyle
rovainadoyle@gmail.com

R. L. Doyle Centro de Pesquisa em Saúde Animal, Instituto de Pesquisas Veterinárias Desidério Finamor (IPVDF), Estrada do Conde, 6000. Eldorado do Sul, RS, Brasil, CEP 92990-00.

Sabrina Braga Knorr[1];
Francine Raimundo da Silva[1];
Camila dos Santos Lagranha[2];
Manoel Roberto Poitevin da Silva Filho[2];
Franklin Gerônimo Bispo Santos[3];
Débora da Cruz Payão Pellegrini[2];
Rovaina Laureano Doyle[1];

[1] *Centro de Pesquisa em Saúde Animal, Instituto de Pesquisas Veterinárias Desidério Finamor (IPVDF), Eldorado do Sul, RS, Brasil.*
[2] *Universidade Federal do Pampa (UNIPAMPA), Uruguaiana, RS, Brasil.*
[3] *Universidade Federal de Alagoas (UFAL), Arapiraca, AL, Brasil.*

ABSTRACT

Background and Objectives: visceral leishmaniasis (VL) is a zoonosis with a major impact on public health, affecting neglected populations, with a high fatality rate, and its control is highly dependent on human actions. This study aimed to describe and compare the level of Knowledge, Attitude, and Practice (KAP) regarding VL in the populations of three municipalities in Rio Grande do Sul (endemic and non-endemic areas). **Methods:** 334 tests were applied, in KAP format, classified as adequate and inadequate. Variable "A" (Attitude) was assessed before and after a brief explanation of the topic. **Results:** among the total number of interviewees, 43.63% in the city with an urban area of endemic focus (UAEF) obtained an adequate score in "K" (Knowledge) about VL, 16.66% with an adequate assessment in "P" (Practice), and 61.40% with an adequate level of "A". In the rural area of endemic focus (RAEF), the scores obtained were 14.54%, 10% and 56.40%, respectively, and in the non-endemic area (NEA), 10.9%, 11.81% and 30.90%, respectively. Respondents with the highest level of "K" in RAEF and UAEF opted for euthanasia for positive dogs and did not change their opinion after the explanation about the disease. In NEA, respondents with the highest "K" score opted for treatment without changing their choice, whereas respondents with the highest "P" score opted for euthanasia and maintained it. **Conclusion:** the results obtained in this study indicate that knowledge of the disease interferes with decision-making regarding it, which can be decisive in VL control and prevention.

Keywords: *Zoonosis. Neglected. Endemic. Score.*

RESUMO

Justificativa e Objetivos: a leishmaniose visceral (LV) é uma zoonose com grande impacto na saúde pública, acometendo populações negligenciadas, com alta taxa de letalidade, sendo seu controle altamente dependente das ações humanas. Este estudo objetivou descrever e comparar o nível de Conhecimento, Atitude e Prática (CAP) em relação à LV nas populações de três municípios do Rio Grande do Sul (zonas de foco endêmico e não endêmico). **Métodos:** foram aplicados 334 questionários, no formato CAP, com resultados classificados em adequado e inadequado. A variável "A" (Atitude) foi avaliada antes e após uma breve explanação sobre o tema. **Resultados:** do total de entrevistados, 43,63% da cidade com zona urbana de foco endêmico (ZUFE) obtiveram escore adequado em "C" (Conhecimento) sobre LV, 16,66%, com avaliação adequada em "P" (Prática), e 61,40%, com nível de "A" adequado. Na zona rural de foco endêmico (ZRFE), os escores obtidos foram 14,54%, 10% e 56,40%, respectivamente, e em zona não endêmica (ZNE), 10,9%, 11,81% e 30,90%, respectivamente. Os respondentes com maior nível de "C" em ZRFE e ZUFE optaram pela eutanásia dos cães positivos e não mudaram de opinião após a explanação sobre a doença. Já em ZNE, os respondentes com maior nível de "C" optaram pelo tratamento sem mudar a escolha, ao passo que os entrevistados com maior escore "P" optaram pela eutanásia e assim a mantiveram. **Conclusão:** os resultados obtidos neste estudo indicam que o conhecimento da doença interfere na tomada de decisão diante da mesma, o que pode ser determinante no controle e prevenção da LV.

Descritores: *Zoonoses. Negligenciadas. Endêmicas. Escore.*

RESUMEN

Justificación y Objetivos: la leishmaniasis visceral (LV) es una zoonosis de gran impacto en la salud pública, provocando trastornos olvidados, con una alta letalidad, y su control depende altamente de la acción humana. Este estudio tuvo como objetivo describir y comparar el nivel de Conocimiento, Actitud y Práctica (CAP) en relación a la LV en las poblaciones de tres municipios de Rio Grande do Sul (áreas endémicas y no endémicas). **Métodos:** se aplicaron 334 cuestionarios, en formato CAP, clasificándose los resultados como adecuados e inadecuados. La variable "A" fue evaluada antes y después de una breve explicación sobre el tema. **Resultados:** del total de entrevistados, el 43.63% de la ciudad con zona urbana de foco endémico (ZUFE) obtuvo una puntuación adecuada en "C" (Conocimiento) sobre VL, el 16.66%, con una evaluación adecuada en "P" (Práctica), y el 61,40%, con un nivel adecuado "A". En la zona rural de foco endémico (ZRFE), los puntajes obtenidos fueron 14,54%, 10% y 56,40%, respectivamente, y en la zona no endémica (ZNE), 10,9%, 11,81% y 30,90% respectivamente. Los encuestados con el nivel más alto de "C" en ZRFE y ZUFE optaron por la eutanasia de los perros positivos y no cambiaron de opinión tras la explicación sobre la enfermedad. En ZNE, los encuestados con la puntuación "C" más alta optaron por el tratamiento sin cambiar su elección, mientras que los encuestados con la puntuación "P" más alta optaron por la eutanasia y la mantuvieron. **Conclusión:** los resultados obtenidos en este estudio indican que el conocimiento de la enfermedad interfiere en la toma de decisiones sobre la misma, lo que puede ser decisivo en el control y prevención de la LV.

Palabras Clave: *Zoonosis. Desatendida. Endémica. Puntuación.*

INTRODUCTION

Leishmaniasis is a zoonosis with a major impact on public health and represents a complex of diseases with a broad clinical spectrum and epidemiological diversity. According to the World Health Organization (WHO), leishmaniasis is among the six most important infectious diseases affecting neglected populations, due to the high incidence of infection, the high lethality of the visceral form when left untreated, the difficult treatment and the capacity to produce deformities. It is estimated that 350 million people are at risk of contracting the infection, with approximately two million new cases of the different clinical forms recorded each year. In Brazil, the country responsible for the majority of cases recorded in Latin America, visceral leishmaniasis (VL) is an emerging disease with an increasing lethality rate.[1-4]

Due to the multifactorial nature of human visceral leishmaniasis (HVL) and canine visceral leishmaniasis (CVL), exposed populations play a decisive role in disease prevention. Therefore, for the health system to perform better, it is essential to identify how the exposed population perceives and behaves when faced with issues related to the disease. In this regard, the use of epidemiological tools, such as questionnaires that aim to characterize Knowledge, Attitude and Practice (KAP), can provide information that helps prevent and control the spread of the disease. Therefore, this study aimed to compare the KAP of populations from three municipalities in Rio Grande do Sul with different epidemiological characteristics.[5-7]

The first autochthonous case of HVL in the state of Rio Grande do Sul occurred in 2009, in the municipality of São Borja. Between 2011 and 2022, Rio Grande do Sul registered 398 notifications of suspected cases of HVL, of

which 53 were confirmed (43 cases are autochthonous) and seven evolved to death.[5-8]

Porto Alegre is the capital of the state of Rio Grande do Sul, with an area of 495,390 km², density of 2,689,94 inhabitants/km² and a population of 1,332,570 inhabitants. The city has a peculiar epidemiological situation, since the urban cycle vector was not found in the studies carried out to date, but rather the sylvatic cycle vectors, which justifies a more detailed study, mainly in relation to health education around the communities that are in an endemic area, since they belong to areas of social vulnerability. In this study, Porto Alegre is treated as a rural area of endemic focus (RAEF).[9]

At the same time, on the western border of RS, the municipality of Uruguaiana recorded the first autochthonous case of CVL in 2009 and, in 2011, the first case of HVL. Uruguaiana is located in the extreme west of the state, 632 km from the capital, with a population of 117,210 inhabitants, a population density of 20.56 inhabitants/km² and an area of 5,702,098 km². In this city, there is a presence of urban-cycle sandflies. and the disease is present in the city's neighborhoods, being used in this study as an urban area of endemic focus (UAEF).[10-12]

The municipality of Eldorado do Sul, in turn, is 15 km from the capital, and has a population of 39,559 inhabitants distributed in an area of 509,614 km² and a population density of 77.63 inhabitants/km². To date, there are no records of the presence of the vector nor data regarding positive dogs and the presence of the disease in humans in Eldorado do Sul. In this study, the municipality will be treated as a non-endemic area (NEA).[13]

METHODS

A total of 334 questionnaires were administered in 110 interviews in Porto Alegre, 110 in Eldorado do Sul and 114 in Uruguaiana, during May and July 2019. The database was obtained by convenience from individual interviews with residents in the aforementioned municipalities, after signing the Informed Consent Form, completed in two copies, with one remaining with the interviewee. As a selection criterion, the interviewees were people over 18 years of age, resident in the chosen regions and who agreed to answer the questionnaire.

The area selected for application of the questionnaires in Porto Alegre (RAEF) was the Protásio Alves neighborhood, where deaths from HVL were reported.[8] The selected locations in Uruguaiana (UAEF) were the neighborhoods of Centro and Mascarenhas de Moraes. In these locations, there were reports of dogs serologically positive for CVL and HVL.[12] The Sans Souci and Progresso neighborhoods were the areas selected for the study in Eldorado do Sul (NEA) and the municipality did not report cases of CVL and HVL until this study was carried out.

Prior to application, the questionnaire was adapted with 30 interviewees, which corresponded to approximately 10% of the total number (n=334).

The questionnaire was divided into three parts, with the aim of identifying the population's KAP. The variables "K" and "P" were assessed through a score, in which the answer considered "correct" received the maximum score (three), and the "incorrect", the minimum score (zero). Nine questions were asked to assess "K", all with open-ended answers, and thirteen questions to characterize "P".

The variable "A", in turn, was assessed through the single question "What do you think should be done with a dog diagnosed positive for leishmaniasis?", with a score of three being given for the answer euthanasia, a score of two for treatment and a score of one for those who did not know how to answer.

In this study, the responses were classified as adequate or inadequate using the sum of the scores obtained in each question of each of the parts. Respondents who obtained from half of the score to the maximum score were classified as adequate (> 32 for "K"; and > 20 for "P"), and those who did not reach these values were classified as inadequate in relation to "K" and "P". In the variable "A", the respondent who opted for euthanasia of the dogs, according to the guidelines contained in the Brazilian Ministry of Health manual of surveillance and control of VL, was considered adequate.[14]

After completing the questionnaires, explanatory information about CVL/HVL was provided and a brief explanation was given on the topic. Then, the single question regarding "Attitude" was asked again to assess whether interviewees, after reading the information, would change their opinion.

For statistical analyses, the responses' qualitative/quantitative variables were associated with each other: location (endemic or non-endemic area) versus KAP and level of Knowledge (K) versus Attitude (A) and Practice (P) of interviewees.

Data analysis was performed based on the frequencies of the questionnaire responses (chi-square) and the score obtained in the KAP (Kruskal-Wallis), using the Statistical Package for the Social Sciences (SPSS) 20 program and a significance level of 5%. In this study, KAP were classified as adequate and inadequate, according to the Brazilian Ministry of Health manual of surveillance and control of VL.[14]

This study was conducted in accordance with the ethical standards required by Resolutions 466/2012, 510/2016 and 580/2018 of the Ministry of Health, being submitted to the *Plataforma Brasil* and approved by the Research Ethics Committees of *Hospital Moinhos de Vento* (HMV), Opinion 3.280.282, on 04/24/2019.

RESULTS

In the first part of the questionnaire, the target populations were characterized. Table 1 summarizes the results of respondents' descriptive analysis.

This study indicates that most respondents in the city of Porto Alegre had completed elementary school (61.8%) and, in the cities of Eldorado do Sul and Uruguaiana, high school (46.5% and 52.7%). In Porto Alegre and Uruguaiana, most respondents reported an income of up to 1 minimum wage (55.5% and 43.9%) and, in

Table 1. General characteristics of the population interviewed in the sampled municipalities.

VARIABLE	ENDEMIC AREAS		NON-ENDEMIC AREA
	RURAL Porto Alegre	URBAN Uruguaiana	Eldorado do Sul
Sex	**N (%) 110**	**N (%)114**	**N (%)110**
Male	33 (30%)	72 (63.2%)	44 (40%)
Female	77 (70%)	42 (36.8%)	66 (60%)
Education	**N (%)**	**N (%)**	**N (%)**
Illiterate	4 (3.6%)	0 (0%)	2 (1.8%)
Elementary school	68 (61.8%)	40 (35.1%)	27 (24.6%)
High school	31 (28.2%)	53 (46.5%)	58 (52.7%)
Higher education	7 (6.4%)	21 (18.4%)	23 (20.9%)
Family income	**N (%)**	**N (%)**	**N (%)**
Up to 1 minimum wage	61 (55.5%)	50 (43.9%)	15 (13.6%)
2-3 minimum wages	23 (20.9%)	28 (24.6%)	27 (24.5%)
Above 3 minimum wages	3 (2.7%)	7 (6.1%)	24 (21.8%)
Total respondents	87 (79.1%)	85 (74.6%)	66 (59.9%)
Branch of labor activity	**N (%)**	**N (%)**	**N (%)**
Does not work	14 (12.7%)	20 (17.5%)	15 (13.6%)
Formal work	59 (53.6%)	56 (49.1%)	83 (75.5%)
Informal work	37 (33.6%)	38 (33.3%)	12 (10.9%)

Eldorado do Sul, the majority chose not to report their monthly income (59.9%). In the three cities studied here, most respondents reported being in the formal labor market (Table 1).

Concerning "Knowledge", in UAEF, Uruguaiana, 88.6% (n=101) declared to know about VL (Table 2). However, in RAEF, in Porto Alegre, the percentage of interviewees who responded to knowing about the disease reached 42.7% (n=47), similar to that observed in Eldorado do Sul (NEA), with 45.5% (n=50) (Table 2).

When assessing the way knowledge about VL was acquired, in Uruguaiana, 41.2% (n=47) reported it through informal conversation, while 17.5% (n=20) reported it through lectures by community workers and 24.6% (n=28) reported it through other means of communication (TV, internet radio). Porto Alegre and Eldorado do Sul presented similar frequencies in this question, with the majority reporting acquiring knowledge through other means of communication, with 23.6% and 25.5%, respectively (Table 2).

Regarding knowledge about the severity of the disease for the canine population, the highest frequency was observed in Uruguaiana (n=99, 86.8%), followed by Eldorado do Sul (n=40, 36.4%) and Porto Alegre (n=33, 30%). At the same time, as for the importance of VL for human health, 78.1% (n=89) of interviewees stated that they knew about the severity of the disease, however, in Porto Alegre and Eldorado do Sul, the majority of individuals did not answer this question (Table 2).

In Uruguaiana (UAEF), approximately 60% of respondents reported knowing the transmitter of VL, of which 56.5% stated that the vector was the phlebotomine or its popular names in Brazil, such as *mosquito-palha*, *anjinho*, *cangalhinha* (open response). Most populations of Porto Alegre (RAEF) and Eldorado do Sul (NEA) (56.4% and 78.2%, respectively) did not know who transmitted the disease, and more than half of respondents did not know who the transmitter of VL was, with 14.5% and 16.4%, respectively (Table 2).

In the second part of the questionnaire, the population's "Practice" in relation to leishmaniasis were assessed (Table 3). Regarding disease prevention, the three populations studied, for the most part, did not use repellent collars on their dogs, with 62.7% of respondents being from Porto Alegre, 59.6% from Uruguaiana and 60.9% from Eldorado do Sul.

Concerning veterinary care, (n=54) 49.1% of respondents from Porto Alegre reported that their dogs did not receive care. In Uruguaiana and Eldorado do Sul, respondents stated that their dogs received care, with 55.3% and 53.6%, respectively (Table 3).

Regarding mosquito control, most of interviewees in our study reported carrying out some form of home or peridomestic monitoring. The main strategy employed was the use of insecticides. Furthermore, most of respondents stated that they did not raise chickens, pigs or wild animals (Table 3).

About the assessment of attitudes toward the disease, each interviewee was asked about the stance they would take if a dog was diagnosed with CVL (Table 4). This question was asked before and after a technical explanation by the interviewer about the disease. In Porto Alegre, before the explanation about VL, the majority, 58.2% (n=64), stated that they were unaware of any contingency protocol in case the disease was confirmed in the animal, but when the question was asked again after the explanation, the majority of respondents, 56.4% (n=62), opted for euthanasia of the animal. In Uruguaiana, the majority, 57% (n=65), initially reported opting for treatment, but after the educational intervention, they decided to euthanize the animal, 61.4% (n=70).

In Eldorado do Sul, there was no change in the main

Table 2. Frequency of responses obtained regarding Knowledge (K) of visceral leishmaniasis in the municipalities studied.

QUESTION	ENDEMIC AREAS		NON-ENDEMIC AREA
	RURAL Porto Alegre N (%)	URBAN Uruguaiana N (%)	Eldorado do Sul N (%)
Have you ever heard of leishmaniasis?			
Yes	47 (42.7%)	101 (88.6%)	50 (45.5%)
No	62 (56.4%)	11 (9.6%)	59 (53.6%)
Not sure	1 (0.9%)	2 (1.8%)	1 (0.9%)
Do you think leishmaniasis is an important disease?			
1	3 (2.7%)	4 (3.5%)	3 (2.7%)
2	0 (0%)	0 (0%)	0 (0%)
3	6 (5.5%)	9 (7.9%)	3 (2.7%)
4	6 (5.5%)	13 (11.4%)	10 (9.1%)
5	33 (30%)	77 (67.5%)	35 (31.8%)
I do not know	62 (56.4%)	11 (9.6%)	59 (53.6%)
How did you acquire this knowledge?			
Informal conversation	12 (10.9%)	47 (41.2%)	16 (14.5%)
Health workers	21 (19.1%)	18 (15.8%)	8 (7.3%)
Lectures by community workers	2 (1.8%)	20 (17.5%)	7 (6.4%)
Other means of communication (TV, newspaper, internet)	26 (23.6%)	28 (24.6%)	28 (25.6%)
Not acquired	1 (0.9%)	1 (0.9%)	1 (0.9%)
I prefer not to answer	48 (43.6%)	0 (0%)	50 (45.5%)
Did you know that leishmaniasis is severe for dogs?			
Yes	33 (30%)	99 (86.8%)	40 (36.4%)
No	76 (69.1%)	12 (9.7%)	69 (62.6%)
Not sure	1 (0.9%)	3 (2.6%)	1 (0.9%)
Did you know that leishmaniasis is severe for humans?			
Yes	36 (32.7%)	89 (77.4%)	38 (34.5%)
No	63 (66.4%)	25 (21.7%)	71 (64.6%)
Not sure	1 (0.9%)	0 (0%)	1 (0.9%)
Do you know anyone who has had the disease?			
Yes	15 (13.6%)	7 (6.3%)	15 (13.0%)
No	95 (86.4%)	100 (87.0%)	95 (86.4%)
I prefer not to answer	0 (0%)	7 (6.1%)	0 (0%)
Do you know who transmits this disease?			
Yes	43.6%	60.9%	21.8%
No	56.4%	39.1%	78.2%
Who? Answer: phlebotomine sandfly or its popular names	14.5%	56.5%	16.4%

Note: through the Kruskal-Wallis test, with a p value>0.001.

Table 3. Frequency of responses obtained on "Practice" (P) for controlling and preventing visceral leishmaniasis.

QUESTION	ENDEMIC AREAS		NON-ENDEMIC AREA
	RURAL Porto Alegre N (%)	URBAN Uruguaiana N (%)	Eldorado do Sul N (%)
Did they use repellent collars on their dogs?			
Yes	11 (10%)	21 (18.4%)	12 (10.9%)
No	69 (62.7%)	68 (59.6%)	67 (60.9%)
No dog	30 (27.3%)	25 (21.9%)	31 (28.2%)
How often did they replace it?			
Up to 8 months	2 (1.8%)	17 (14.9%)	9 (8.2%)
More than 8 months	7 (6.4%)	5 (4.4%)	5 (4.5%)
Do not use	101 (91.8%)	92 (80.7%)	96 (87.3%)
Do dogs have veterinary care?			
Yes	26 (23.6%)	63 (55.3%)	59 (53.6%)
No	54 (49.1%)	27 (23.7%)	19 (17.3%)
No dog	30 (27.3%)	24 (21.1%)	32 (29.1%)
Do you carry out any mosquito control at home or in the yard?			
Yes	55 (50%)	89 (78.1%)	63 (57.3%)

Do you use repellent on people?			
Yes	32 (29.1%)	54 (47.4%)	52 (47.3%)
Do you use insecticides to control mosquitoes at home?			
Yes	61 (55.5%)	79 (69.3%)	85 (77.3%)
Raise of:			
Chickens	20 (18.2%)	5 (4.4%)	4 (3.6%)
Pigs	1 (0.9%)	1 (0.9%)	2 (1.8%)
Horses	0 (0%)	6 (5.26%)	5 (4.54%)
Wild animals	5 (4.5%)	2 (1.8%)	9 (8.2%)

Table 4. Characterization of the "Attitude" (A) of respondents if their dog was diagnosed positive for visceral leishmaniasis, before and after the explanation about the disease.

OPTIONS	ENDEMIC AREAS		NON-ENDEMIC AREA
	RURAL Porto Alegre N (%)	URBAN Uruguaiana N (%)	Eldorado do Sul N (%)
BEFORE the explanation			
Treatment	26 (23.6%)	65 (57%)	52 (47.3%)
Euthanasia	20 (18.2%)	34 (29.8%)	15 (13.6%)
Unknown	64 (58.2%)	15 (13.2%)	43 (39.1%)
AFTER the explanation			
Treatment	28 (25.5%)	41 (36%)	75 (68.2%)
Euthanasia	62 (56.4%)	70 (61.4%)	34 (30.9%)
Unknown	20 (18.2%)	3 (2.6%)	1 (0.9%)

Note: through the Kruskal-Wallis test, with a p value =0.007.

Table 5. Classification of Knowledge (K), Attitude (A) and Practices (P) of the population sampled in the cities of Porto Alegre, Uruguaiana and Eldorado do Sul in relation to visceral leishmaniasis as adequate and inadequate.

KAP	ENDEMIC AREAS		NON-ENDEMIC AREA
	RURAL Porto Alegre N (%)	URBAN Uruguaiana N (%)	Eldorado do Sul N (%)
Knowledge (K)			
Inadequate (up to 32)	94 (85.45%)	66 (57.89%)	98 (89.1%)
Adequate (33-66)	16 (14.54%)	48 (43.63%)	12 (10.9%)
Practice (P)			
Inadequate (up to 20)	99 (90%)	95 (83.33%)	97 (88.18%)
Adequate (21-42)	11 (10%)	19 (16.66%)	13 (11.81%)
Attitude (A) - Before the technical explanation			
Adequate (euthanasia)	20 (18.2%)	34 (29.8%)	15 (13.6%)
Inadequate (treatment/not sure)	90 (81.8%)	80 (70.2%)	95 (86.4%)
Attitude (A) - After the technical explanation			
Adequate (euthanasia)	62 (56.4%)	70 (61.4%)	34 (30.9%)
Inadequate (treatment/not sure)	48 (43.7%)	44 (38.6%)	76 (69.1%)

response even after the interviewer's explanation about VL, with the majority responding that they would opt for treatment, both before (47.3%, n=52) and after (68.2%, n=75) the explanation (p<0.001) (Table 4).

In the assessment of the level of KAP, most respondents presented "Knowledge" (K) considered inadequate in the three municipalities. "Attitude" (A) was categorized as adequate in Uruguaiana, whereas, in Porto Alegre and Eldorado do Sul, it was classified as inadequate, even after the explanation (Table 5).

Through the Kruskal-Wallis test, with a p value>0.001 in K and P in the 3 cities and A with p=0.007.

DISCUSSION

In characterizing the populations studied, we found variations in the level of education of interviewees. In a study carried out in the state of Mato Grosso do Sul, the majority (48%) of interviewees declared having completed elementary school. In Belo Horizonte (MG), 41.5% declared having only elementary school. However, 77% of interviewees in the Metropolitan Region of Belo Horizonte had completed elementary school, similar to the results found in our study in the region of Porto Alegre (RAEF), while the results in Uruguaiana (UAEF) and Eldorado do Sul (NEA) were similar to those observed in

the state of Maranhão, where 48.5% of respondents had completed elementary school.[5,15-17]

As for income, in the municipality of Raposa (MA), 47.6% of respondents reported an income of up to 1 minimum wage, similar to a study conducted in João Pessoa (PB), in which 47.8% of respondents reported an income of 1 minimum wage. On the Island of São Luís (MA), 89% of the population studied reported an income of up to 2 minimum wages, as they receive federal government aid grants, quite different from the results described here, in which respondents who reported receiving between 2 and 3 minimum wages represented between 20.9% and 24.6% of the total.[18-20]

In relation to formal work, studies carried out in the metropolitan region of Belo Horizonte (46%) and in Ethiopia (31.5%) support our results, in which the majority of interviewees were included in the formal labor market.[5,6]

As for knowledge of the disease, most interviewees in Uruguaiana stated that they were aware of it, as in other studies conducted in other cities considered endemic for VL. The majority of the population studied had already heard of the disease, as in a study conducted in the city of Três Lagoas (MS), in which 100% of respondents were aware of it. In an equivalent study in the metropolitan region of Belo Horizonte (RMBH-MG), 84% of interviewees were aware of VL. The presence of the vector and the history of notifications of VL cases widely distributed in the urban area of Uruguaiana suggest that the population of the municipality had prior knowledge of the disease, in contrast to the results obtained in Porto Alegre.[5-21] Radio and television were considered the main sources of information about the disease both in our study and in two others carried out in RMBH-MG.[5-22]

Regarding the population's knowledge about the severity of the disease for dogs, our results in UAEF (9.73%) were similar to those found in Belo Horizonte (MG), where less than 10% of respondents did not know about the relationship with dogs. However, they differed from the results RAEF and NEA, where more than 60% of respondents were unaware of the importance of dogs. Likewise, our respondents living in urban areas had much greater knowledge about the severity for humans than those in rural or non-endemic regions. However, in a study conducted in Paraguay, no respondent stated that they knew about the severity of VL for humans.[7,16]

When asked if they knew anyone who was sick, the majority of our interviewees responded negatively, in contrast to a study conducted in Maranhão, in which 57.8% of interviewees reported having known someone who was sick.[17]

The fact that the city of Uruguaiana has been living with the disease in urban areas for a longer period of time is reflected in the knowledge of the majority of the population studied regarding the vector of VL found in our study and previously described by Massia *et al*. in the same city. This is different from the situation observed in Belo Horizonte, an endemic area of VL, where less than 5% of the population studied indicated the correct vector. Regarding VL prevention practices, the use of repellent collars is still not accessible for the populations we studied, in the same way that another study conducted in Uruguaiana indicated that more than 73.66% of the population assessed stated that they were financially insufficiency to purchase insecticide collars.[12,16]

The use of insecticides at home is practiced by the majority of the population we studied. In a similar study in Belo Horizonte, respondents used repellents mainly during feeding times for vectors. In Ethiopia, the majority of respondents used mosquito nets as their main method of insect control.[6,16]

In the three municipalities we studied, most respondents stated that they did not raise chickens, pigs or wild animals, as was the case in Belo Horizonte (MG), where the majority of respondents (80%) also stated that they did not raise these animals. Studies in São José do Ribamar (MA) and Belo Horizonte (MG) indicated that raising chickens can create an environment that is favorable to the multiplication of sand flies, due to the organic waste generated by these animals.[16,23,24]

Concerning the attitude to be taken if a dog was sick, the significant increase in the option for euthanasia after the educational intervention in the two endemic areas of this study suggests that respondents understood the severity of the disease and that dogs are the main domestic reservoir of VL and that it is present in these locations, with canine and human deaths. This supports a study carried out in Birigui (SP), in which 65% of respondents responded that euthanasia would be the best option and, after the intervention, 85% opted for euthanasia. In a study carried out in Paraguay, 63.6% of respondents would euthanize their animal if it were diagnosed positive for the disease.[7,25]

In relation to the categorization of the KAP level, most of our respondents presented "Knowledge" (K) considered inadequate in the three municipalities, similarly to a study carried out in Ribeirão das Neves (MG). However, in a study in Ethiopia, most of interviewees had adequate levels of knowledge and practice in relation to VL. In Minas Gerais, the level of knowledge was adequate in non-endemic areas and inadequate in endemic areas, suggesting that there is no linear relationship between knowledge and practices.[5,6,22]

Our study indicated an inadequate KAP score in the three cities sampled in the research. The municipality of Uruguaiana presented a better KAP score, and this finding can be attributed to the spread of the disease and the vector in the urban area of the municipality, monitoring of the disease, in addition to constant visits of health workers to clarify information about the disease (informal communication from interviewees), which leads us to believe that this enabled a higher level of KAP in this population. [26,27,28]

In the variable "Attitude" (A), the interviewees from Porto Alegre and Uruguaiana obtained an adequate score, which can be attributed to the fact that in these municipalities in endemic areas there are canine and human cases with deaths, which did not occur in Eldorado do Sul.

Since this is a study in which data collection de-

pends on participant participation, the results may not represent the populations assessed. However, most of the population in the three municipalities studied did not have adequate knowledge and practices, reinforcing the need for public policies aimed at health education and the adoption of prophylactic measures to prevent and control this neglected disease.

Most of the population in the three municipalities studied did not have adequate knowledge and practices, reinforcing the need for public policies aimed at health education and the adoption of prophylactic measures to prevent and control this neglected disease.

The results obtained in this study contribute to better combating this zoonosis in endemic regions and bringing pertinent information closer to non-endemic regions, thus preventing this disease.

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AUTHORS' CONTRIBUTIONS

Sabrina Braga Knorr contributed to project execution, literature search, writing of the abstract, introduction, methodology, discussion, interpretation and description of results, conclusions and statistics. **Francine Raimundo da Silva** contributed to writing of the abstract, review and statistics. **Camila dos Santos Lagranha** contributed to writing of the abstract, review and statistics. **Manoel Roberto Poitevin da Silva Filho** contributed to writing of the abstract, review and statistics. **Franklin Gerônimo Bispo Santos** contributed to project administration, literature search, writing of the abstract, introduction, methodology, discussion, interpretation and description of results, conclusions, review and statistics. **Débora da Cruz Payão Pellegrini** contributed to project administration, literature search, writing of the abstract, introduction, methodology, discussion, interpretation and description of results, conclusions, review and statistics. **Rovaina Laureano Doyle** contributed to project administration, literature search, writing of the abstract, introduction, methodology, discussion, interpretation and description of results, conclusions, review and statistics.

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

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ORIGINAL ARTICLE

Assessment of technique and adherence to hand hygiene in the central of materials and sterilization center

Avaliação da técnica e adesão à higiene de mãos no centro de materiais e Esterilização

Evaluación de la técnica y adherencia a la higiene de manos en el centro de materiales y esterilización

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Corresponding Author:
André Luiz Silva Alvim
andrealvim1@ufjf.br

Address: Av. José Lourenço Kelmer, s/n, São Pedro, Juiz de Fora, Minas Gerais, Brasil.

Bruno Henrique Ataíde da Trindade[1];
Vanessa Albuquerque Alvim de Paula[1];
Thiago César Nascimento[1];
Thais Vidal de Oliveira[1];
Braulio Roberto Gonçalves Marinho Couto[2];
André Luiz Silva Alvim[1];

[1] Universidade Federal de Juiz de Fora, Juiz de Fora, MG, Brazil.
[2] Biobyte Systems, Belo Horizonte, MG, Brazil.

ABSTRACT

Background and Objectives: Hand hygiene should be encouraged among the nursing team of the materials and sterilization center, as various processes can be sources of microorganism transmission. The objective is to assess the quality of hand hygiene technique and adherence in the materials and sterilization center, according to the recommendations of the World Health Organization. **Methods:** This is an observational, descriptive, and prospective study, in which weekly visits were conducted from February to May 2023. On-site direct observation was used, followed by notes on an adapted form. **Results:** Out of 364 observations made, only 91 (25%) performed hand hygiene, and only 7 (1.9%) executed the correct technique. Moments with the highest adherence were upon arrival at the unit (35.1%), upon leaving the unit (12.1%), and before handling packaging and health products. Among the supplies used, liquid soap had the highest frequency (51.6%). Males showed higher adherence compared to females ($p<0.01$). **Conclusion:** Adherence to hand hygiene was low among the nursing staff, and few executed the correct technique according to the steps recommended by the World Health Organization. The results underscore the need for awareness-raising and training actions regarding this preventive measure in the materials and sterilization center.

Keywords: *Hand disinfection. Sterilization. Nursing. Infection Control.*

RESUMO

Justificativa e Objetivos: A higienização das mãos deve ser incentivada entre a equipe de enfermagem do centro de materiais e esterilização, uma vez que diversos processos podem ser fontes de transmissão de microrganismos. O objetivo é avaliar a qualidade da técnica e adesão à higiene de mãos no centro de materiais e esterilização de acordo com as recomendações da Organização Mundial da Saúde. **Métodos:** Este é um estudo observacional, descritivo e prospectivo, no qual foram realizadas visitas semanais durante o período de fevereiro a maio de 2023. Utilizou-se observação direta no local e, posteriormente, foram feitas anotações em um formulário adaptado.

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Resultados: No total de 364 observações realizadas, apenas 91 (25%) realizaram a higienização das mãos, e somente 7 (1,9%) executaram a técnica correta. Os momentos com maior adesão foram ao chegar à unidade (35,1%), ao sair da unidade (12,1%) e antes de manusear embalagens e produtos para a saúde. Entre os insumos utilizados, o sabonete líquido obteve maior frequência (51,6%). O sexo masculino apresentou maior adesão quando comparado ao feminino (p<0,01). **Conclusão:** A adesão à higiene de mãos foi baixa entre a equipe de enfermagem e poucos realizaram a técnica correta de acordo com os passos recomendados pela Organização Mundial da Saúde. Os resultados reforçam a necessidade de ações de sensibilização e treinamento em relação a esta medida preventiva no centro de materiais e esterilização.

Descritores: *Desinfecção das mãos. Esterilização. Enfermagem. Controle de Infecções.*

RESUMEN

Justificación y Objetivos: La higiene de manos debe ser fomentada entre el personal del centro de materiales y esterilización, ya que varios procesos pueden ser fuentes de transmisión de microorganismos. El objetivo de este estudio es evaluar la calidad de la técnica y la adherencia a la higiene de manos en el centro de materiales y esterilización según lo recomendado por la Organización Mundial de la Salud. **Métodos:** Este es un estudio observacional, descriptivo y prospectivo, en el cual se realizaron visitas semanales durante el período de febrero a mayo de 2023. Se utilizó la observación directa en el lugar y, posteriormente, se realizaron notas en un formulario adaptado. **Resultados:** De un total de 364 observaciones realizadas, solo 91 (25%) realizaron la higiene de manos, y solo 7 (1,9%) ejecutaron la técnica correcta. Los momentos con mayor adherencia fueron al llegar a la unidad (35,1%), al salir de la unidad (12,1%) y antes de manipular envases y productos de salud. Entre los suministros utilizados, el jabón líquido tuvo la mayor frecuencia (51,6%). Los hombres mostraron una mayor adherencia en comparación con las mujeres (p<0,01). **Conclusión:** La adherencia a la higiene de manos fue baja entre el personal de enfermería y pocos ejecutaron la técnica correcta según lo recomendado por la Organización Mundial de la Salud. Los resultados refuerzan la necesidad de acciones de sensibilización y capacitación con respecto a esta medida preventiva en el centro de materiales y esterilización.

Palabras Clave: *Desinfección de manos. Esterilización. Enfermería. Control de Infecciones.*

INTRODUCTION

Health Care-Related Infections (HCRI) are defined as those acquired and/or manifested by the patient during the hospitalization period or after discharge, becoming a problem for health services, because they are associated with increased morbidity and mortality.[1] These infections are transmitted by direct and indirect contact, droplets and aerosols, being closely linked to the care that the patient receives, as well as to the hands of health professionals, considered one of the main sources of microorganism dissemination.[2]

In this context, hand hygiene (HH) emerges as a low-cost preventive measure and high capacity to prevent and reduce HCRI, constituting itself as an indicator of quality of care, especially concerning patient safety.[3] Accordingly, in 2009, the World Health Organization (WHO) released the Multimodal Strategy for Improving Hand Hygiene guide containing relevant tools to assist in the implementation of programs aimed at increasing adherence rates and the effectiveness of the technique in health services.[4]

HH is recommended by the WHO at five times during the assistance provided: before contact with the patient, before aseptic procedures, after exposure to organic fluids, after contact with the patient and after contact with the environment where the patient is.[5] The importance of hand hygiene and corresponding actions during observed moments extends beyond the sectors directly involved in direct patient care, reaching also the support sectors that perform indirect functions in the assistance, such as the Materials and Sterilization Center (MSC).

MSC is referred to as a unit responsible for the processing of Health Products (HP), which performs cleaning, inspection, preparation, sterilization or disinfection, storage and distribution for surgical, outpatient and care units, contributing to a safe practice of care. In this support sector, HH should be encouraged among the nursing staff, since several processes can be sources of transmission of microorganisms to the HP.[6]

A cross-sectional study highlighted that, among the moments with pre-established indications for hand hygiene at the sterilization center, only two reached a rate above 50%: at the beginning of the work shift and after removing the gloves.[7] However, the literature still needs to advance in research on the subject, since the research gap refers to the evaluation of this preventive measure, which is directly related only to adherence, without reporting the quality of the technique following the steps recommended by WHO.

This research presents the following guiding questions: Does the nursing team of MSC have a good adherence to hand hygiene? Is the quality of the technique in accordance with the steps recommended by WHO? Thus, the present study is necessary to evaluate this practice in the support sector, since the hands of professionals are directly linked to their health by dealing with conta-

minated products and with the users of the service, because they constitute a potential source of transmission of microorganisms that may exceed the final minimum biological load, even after all HP processing.

The objective of this study is to evaluate the quality of technique and adherence to hand hygiene in the materials and sterilization center, according to the recommendations of the World Health Organization.

METHODS

Design

This is an observational, descriptive and prospective study of a quantitative nature, conducted at the MSC of a public hospital in Juiz de Fora, MG, Brazil. This research used the tool STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) to guide the construction of methodological steps.[8]

Studied scenario

The hospital is exclusively intended for users of the Unified Health System (UHS) and performs outpatient procedures and high complexity surgeries in the region of Zona da Mata, MG. The MSC is responsible for processing local health products and has an infrastructure that includes an ultrasonic washer and two autoclaves. Standard Operating Procedures (SOP) are available for digital consultation, and training is established according to a schedule prepared by the nurse responsible for the sector.

Population

A sample calculation was performed by the Epi Info™ version 7 software to determine the number of observations necessary to achieve the study objectives. The reference population used by the researchers was the average of sterilized HP per month, given the interrelationship between the management of each item by professionals and the prevention of HCRI, including HH. In this scenario, the population size was the average of 6,899 products per month, with an expected frequency of 50%, a sampling error of 5% and a confidence interval of 95%; thus, the minimum sample required was 364 observations. All HH observations were conducted in a population composed of three nurses and 18 nursing technicians.

Selection criteria

The inclusion criteria were: involvement in any phase of processing of HP and appropriate use of institutional identification badge. Maintenance technicians of autoclaves and nursing students were excluded.

Data collection

The data collection was carried out by the researchers themselves in the period from February to May 2023, through weekly visits using direct observation on site and, subsequently, annotations in an adapted form, based on the information from a previous study that evaluated HH in the sterilization center.[7] The instrument contained the following variables: professional category (nurses or nursing technicians), sex, shift of work, presence (or not) of ornaments during observation, if the hand hygiene was performed (or not), the input used (liquid soap and/or alcohol preparation) and finally the correct technique was performed according to the six steps recommended by WHO.[5] To reduce the Hawthorne effect, which refers to the change in people's behavior due to awareness of being evaluated, unidentified observation and visit at non-scheduled times were adopted.[9]

Data analysis

The data were analyzed by means of simple descriptive statistics to present absolute and relative values about the data collection instrument. The chi-square test, and when necessary, the exact Fisher test, was used to compare the proportions between nominal variables and occupational categories. In this case, the IBM Statistical Package for the Social Sciences version 21 was used. The rate of adherence to HH, as observed by the researchers, was calculated by the following formula: number of HH actions divided by the number of moments observed, multiplied by 100. To calculate the quality of the HH technique, referred to as the proper execution following the six steps of the WHO, the same formula was applied. However, the adherence was considered complete and noted by the researchers only when all items described in the technique were performed by the team.[5]

Ethical considerations

This study was approved by the Research Ethics Committee (REC), under opinion number: 5,660,025 and Certificate of Presentation of Ethical Appreciation (CAAE): 62352022.5.0000.5133, on September 22, 2022. All aspects contained in the Ordinance no 466/2012 and Resolution no 510/2016 of the Ministry of Health were respected.

RESULTS

Of the 364 observations evaluated, only 91 (25.0%) performed hand hygiene and only 7 (1.9%) used the correct technique. It is important to mention that, of the actions observed, 301 were performed by nursing technicians and 63 by nurses. In this sense, a compliance rate of 24.2% was identified, with six actions using the correct technique (2.0%), while nurses' adherence rate was 28.6%, with only one use of the WHO recommended technique (1.6%). Males showed higher adherence to HH when compared to females ($p<0.01$) (Table 1).

The use of liquid soap is the most frequent product when performing the technique (51.6%) and then the alcoholic preparation (44%). Few used the two inputs in a complementary way during the work routine. The use of the product did not have statistical difference between the professional category ($p>0.05$).

In relation to the moments and opportunities observed during hand hygiene practice, there is a higher adherence of the nursing team when arriving at the unit (35.1%), when leaving the unit (12.1%) and before handling packaging and health products (7.6%) (Table 2).

Table 1. Evaluation of hand hygiene technique and adherence in the materials and sterilization center, Juiz de Fora, MG, Brazil. (n=364).

Variables	Obs* (n)	Adherence to HH**			Correct technique, according to WHO		
		Actions performed	Rate of adherence (%)	*p*-value	Actions performed	Rate of adherence (%)	*p*-value
Professional category							
Nurse	63	18	28.6	0.28π	01	1.6	0.65ψ
Nur. Tec.	301	73	24.2		06	2.0	
Overall rate	364	91	25.0		07	1.9	
Sex							
Female	227	43	18.9	0.00 π	03	1.3	0.24 ψ
Male	137	48	35.0		04	2.9	

*Note: *Obs = observations; **HH = hand hygiene; π = Chi-square test; ψ = Fisher's exact test.*

Table 2. Observed moments and actions for hand hygiene in the materials and sterilization center, Juiz de Fora, MG, Brazil. (n=91).

Observed moments	n	%
• When arriving the unit	32	35.1
• When leaving the unit	11	12.1
• Before handling packaging and health products	07	7.6
• After putting on gloves	06	6.6
• Before assembling boxes and trays	05	5.4
• Before handling processed health products (looking for a health product or changing places to clean the shelf)	04	4.4
• After administrative activities (using the telephone, computer and books)	04	4.4
• Before assembling a load of health products in the autoclave	03	3.3
• After checking and recording consignments	03	3.3
• At the beginning of the work shift	03	3.3
• Before storing processed health products	02	2.2
• Before packaging health products (boxes, linens)	02	2.2
• Before distributing health products to the units	02	2.2
• Before distributing health products to the units	01	1.1
• Before removing the load from the autoclave	01	1.1
• After recording the unit's productivity	01	1.1
• After recording contaminated health products received from consumer units*	01	1.1
• After putting on protective gear	01	1.1
• After disinfecting benches	01	1.1
• Before preparing the Bowie and Dick test	01	1.1

DISCUSSION

This study showed that, among the 364 observations recorded by the researchers, 25% included the practice of HH, which worsened when evaluating the quality of the technique according to the steps recommended by the WHO, reaching only 1.9%. Low adherence is reported in the literature not only at the sterilization center, but also in care sectors, describing values that vary from 29% to 38.2%, with more than 400 opportunities observed.[5,10]

In the MSC, there are still several gaps regarding the use of this preventive measure as a strategy for preventing HCRI, as demonstrated in this study. Corroborating, a survey conducted in this support sector reinforced that HH was not valued by the nursing team in the clean area, providing an unsafe practice.[7] This finding highlights the urgent need for targeted interventions to improve adherence and quality of hand hygiene in support sectors that provide indirect patient care.

Regarding the use of the correct technique, only seven (1.9%) did it as recommended by WHO, six being performed by nursing technicians and one by a nurse. A cross-sectional study conducted in the operating room of a public hospital in Natal (Brazil) showed that, out of 28 professionals, 19 had errors in relation to the procedure, violating the standardized step-by-step technique.[2]

This research showed that there was greater adherence by male professionals in relation to HH, when compared to female. The literature does not present a relationship between this variable and adherence, requiring further investigation with other methodological approaches to identify the reasons. It is important to mention that the technique performed at the times recommended by WHO still needs to be improved, which should be interpreted with caution. For this reason, educational strategies, the provision of adequate resources, regular supervision and the establishment of an organizational safety culture are fundamental approaches to promote adherence to hand hygiene among health professionals.[1,3,7-10]

In this sense, the literature seeks alternatives to reduce the complexity of the six steps for HH, proposing to reduce them by half, with a new approach to the execution of the technique. A study compared the two hand hygiene techniques in reducing microbial load (six steps of WHO versus three-step friction), showing that the first, respectively, was more effective in reducing microbial load, which requires reinforcing awareness and demystification actions of the complexity of the technique.[11]

Stratifying the data by professional category, this study points to a difference in the adherence rate between nursing technicians and nurses. However, the aspects that contribute to low adherence should be investigated in the work routine. Although the objective of this research is not to identify the factors that affect hand hygiene, it is highlighted that failures were observed related to infrastructure, as the availability of sinks in places of di-

fficult access and the presence of equipment nearby that hinder the execution of the technique. A study published in 2021 listed some difficulties for adherence to patient safety goals by staff, including HH. Among them, the workload, exhaustion, inexperience, lack of knowledge, short time to perform tasks, forgetfulness and lack of observation of attitudes for safe assistance were cited.[12]

As for the most used inputs, the data show that liquid soap is the main choice by nursing staff, representing 51%, while the use of alcoholic preparation was 44%. Similar results were found in other sectors, such as the Neonatal Intensive Care Unit, where HH with water and soap achieved a compliance rate of 74%, while the use of alcohol preparation reached a low rate of 13%.[13] It is worth mentioning the WHO manual for health service professionals, which describes when it is necessary to use water and liquid soap or, preferably, alcoholic preparations.[5,14]

Evaluating the moments and opportunities for hand hygiene in MSC, the highest rates observed were on arrival and departure of the unit, before handling packaging and other HP. These results are similar to those of a survey conducted in Brazil, which found that, among the moments with pre-established indication for HH, only two indices presented satisfactory rates of adherence to the practice: the beginning of the work shift (when arriving at the unit) and after removing the gloves.[7]

The contribution of this study to clinical practice is linked to the results found in relation to adherence, mainly by following the six-step technique recommended by WHO. The values remained at alarming levels, reinforcing the need for permanent education about HH to reduce HCRI, as already pointed out by other researchers.[15]

This study presented a limitation that should be considered, which is the possible influence of the Hawthorne effect. For this reason, it was recommended the hidden observation as a method of evaluation and the alternation of times for data collection.

This study evaluated the hand hygiene practice and the quality of the technique as recommended by WHO. Among the observations made, the data alert to the need for actions that increase the adherence of nursing staff in the materials and sterilization center. Although liquid soap was the most frequently used by health professionals, it is necessary to implement strategies in the sector that aim to guide how to properly perform the technique and the recommended times for performing this preventive measure during the working day.

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AUTHORS' CONTRIBUTIONS

Bruno Henrique Ataíde da Trindade, Braulio Roberto Gonçalves Marinho Couto and André Luiz Silva Alvim contributed to the bibliographic research, writing of the abstract, introduction, methodology, discussion, interpretation and description of results, preparation of tables, conclusions, review and statistics. **Bruno Henrique Ataíde da Trindade, Vanessa Albuquerque Alvim de Paula, Thiago César Nascimento, Thais Vidal de Oliveira, Braulio Roberto Gonçalves Marinho Couto and André Luiz Silva Alvim** contributed to the writing of the abstract, critical reading of the manuscript, interpretation and review. **Bruno Henrique Ataíde da Trindade, Braulio Roberto Gonçalves Marinho Couto and André Luiz Silva Alvim** contributed to the writing of the abstract, review and statistics.

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

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Revista de Epidemiologia e Controle de Infecção

Hospital Santa Cruz

REVIEW ARTICLE

Structuring and restructuring COVID-19 Intensive Care Units: a systematic review

Estruturação e reestruturação das Unidades de Terapia Intensiva na COVID-19: revisão sistemática

Estructuración y reestructuración de las Unidades de Cuidados Intensivos en COVID-19: revisión sistemática

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Corresponding Author:
Luis Fernando Reis Macedo
luis.reis@urca.br

Address: Rua Cel. Antônio Luiz, 1161- Pimenta, Crato, Ceará, Brasil.

Luis Fernando Reis Macedo[1,2];
Kenya Waléria de Siqueira Coelho Lisboa[1];
Thais Rodrigues de Albuquerque[1];
Alexandre Pazetto Balsanelli[2];
Sarah De Lima Pinto[1];
Izabel Cristina Santiago Lemos de Beltrão[1];
Gyllyandeson de Araujo Delmondes[3];

[1] *Universidade Regional do Cariri (URCA), Crato, CE, Brasil.*
[2] *Universidade Federal de São Paulo (UNIFESP), SP, Brasil.*
[3] *Universidade Federal do Vale do São Francisco (UNIVASF), Petrolina, PE, Brasil.*

ABSTRACT

Background and Objectives: the COVID-19 pandemic imposed restructuring and reorganization in healthcare services, particularly in Intensive Care Units (ICUs), due to the increased demand for hospital care for the thousands of severe cases of the disease. Thus, understanding this ICU reorganization process is useful for healthcare system planning and, consequently, for preventing system collapse in the face of impending pandemics. The objective was to identify elements related to the restructuring and organization of human resources, materials, and organization/structure processes in ICUs during the COVID-19 pandemic. **Methods:** this is a qualitative systematic review. Searches were conducted in the MEDLINE, PubMed, Scopus, Web of Science, and Embase databases. The results were exported to the Rayyan software for subsequent screening and blind selection by two independent researchers as well as for assessing the risk of bias and individual methodological quality of selected studies. **Results:** a total of 171 articles were found across the five databases, with five articles selected to be included in this review. The identified elements concerning the restructuring and organization of ICUs were the use and availability of personal protective equipment, oxygen, and oxygen therapy equipment, medications, psychological support for healthcare professionals, patient safety measures, and space maintenance. **Conclusion:** this review allowed for the compilation and synthesis of necessary elements for the restructuring and organization of ICUs during the pandemic, considering the need for managers to respond swiftly to the high demand brought on by COVID-19.

Keywords: *Intensive Care Units. COVID-19. Hospital Restructuring. Hospital Administration.*

RESUMO

Justificativa e Objetivos: a pandemia de COVID-19 impôs reestruturações e reorganizações nos serviços de saúde, principalmente nas Unidades de Terapia Intensiva (UTIs), devido ao aumento da demanda de assistência hospitalar para os milhares de casos graves da doença. Assim, compreender esse processo de reorganização das UTIs é útil para o planejamento do sistema de saúde e, consequentemente, a prevenção do colapso do sistema na iminência de pandemias. Objetivou-se identificar os elementos relacionados à reestruturação e estruturação dos recursos humanos, materiais e processos de organização/estruturação das UTIs durante a pandemia de COVID-19. **Métodos:** revisão sistemática qualitativa. Buscas foram realizadas nas bases de dados MEDLINE, PubMed, Scopus, *Web of Science* e Embase. Os resultados foram exportados para o *software* Rayyan para posterior triagem e seleção cega por dois pesquisadores independentes, bem como avaliação do risco de viés e da qualidade metodológica individual dos estudos selecionados. **Resultados:** foram encontrados 171 artigos nas cinco bases de dados, tendo sido selecionados cinco para compor esta revisão. Os elementos identificados referentes à reestruturação e estruturação das UTIs foram o uso e disponibilidade de equipamentos de proteção, oxigênio e equipamentos para oxigenoterapia, medicamentos, apoio psicológico aos profissionais, aspectos para a segurança do paciente e manutenção do espaço. **Conclusão:** esta revisão possibilitou unir e sintetizar elementos necessários na reestruturação e estruturação de UTIs durante a pandemia, tendo em vista a necessidade de agilidade entre os gestores em atender a grande demanda exigida na COVID-19.

Descritores: *Unidades de Terapia Intensiva. COVID-19. Reestruturação Hospitalar. Administração Hospitalar.*

RESUMEN

Justificación y Objetivos: la pandemia de COVID-19 impuso reestructuraciones y reorganizaciones en los servicios de salud, especialmente en las Unidades de Cuidados Intensivos (UCIs), debido al aumento de la demanda de asistencia hospitalaria para los miles de casos graves de la enfermedad. Por lo tanto, comprender este proceso de reorganización de las UCIs es útil para la planificación del sistema de salud y, en consecuencia, para prevenir el colapso del sistema en la inminencia de pandemias. El objetivo fue identificar los elementos relacionados con la reestructuración y estructuración de recursos humanos, materiales y procesos de organización/estructuración de las UCI durante la pandemia de COVID-19. **Métodos:** revisión sistemática cualitativa. Se realizaron búsquedas en las bases de datos MEDLINE, PubMed, Scopus, *Web of Science* y Embase. Los resultados se exportaron al *software* Rayyan para la posterior selección y cribado ciego por dos investigadores independientes, así como para la evaluación del riesgo de sesgo y la calidad metodológica individual de los estudios seleccionados. **Resultados:** se encontraron 171 artículos en las cinco bases de datos, cinco de los cuales fueron seleccionados para componer esta revisión. Los elementos identificados respecto a la reestructuración y estructuración de las UCI fueron el uso y disponibilidad de equipos de protección, oxígeno y equipos para oxigenoterapia, medicamentos, apoyo psicológico a los profesionales, aspectos para la seguridad del paciente y mantenimiento del espacio. **Conclusión:** esta revisión permitió unir y sintetizar los elementos necesarios para la reestructuración y organización de las UCIs durante la pandemia, teniendo en cuenta la necesidad de agilidad por parte de los gestores para atender la alta demanda exigida por la COVID-19.

Palabras Clave: *Unidades de Cuidados Intensivos. COVID-19. Reestructuración Hospitalaria. Administración Hospitalaria.*

INTRODUCTION

Infection with the SARS-CoV-2 virus represented a new context for healthcare. Faced with the expectation of increased demand for hospital care, health systems worldwide presented a worrying overload, directly impacting quality of care.[1] Thus, interventions and restructuring of services were necessary, aiming for greater agility and effectiveness in serving the population and seeking to prevent the collapse of health systems in the face of the pandemic,[2] mainly in the absence of effective vaccines and antivirals[3].

As a result, Intensive Care Units (ICUs) had an exponential increase in hospitalizations, indicating urgency in decision-making by health managers. They are in the ICUs, where the necessary support for caring for critical patients is found. In the absence of this hospital sector, a significant risk can be presented to patients when there is a need for hospitalization, as occurred in the calamities faced during the COVID-19 pandemic.[4]

In the case of management in healthcare services, definitions were drawn up on the administration of these resources to assist in the process of coordinating the units, and these are differentiated into: human resources (HR), which concern the protection of the patient, the operator and the population, aspects of care; material resources (MR), which contrast physical-technical factors, quality improvement, equipment and accessories; organization/structure processes, which confront sectoral administrative bureaucratic actions.[5]

The definitions aligned by Coppola[5] are based on benchmarking, a process of studying agreements and analyzing best management practices based on international laws and guidelines.

With this, an understanding of the ICU reorganization process emerged, focusing on Coppola's[5] definitions, which required the remediation of the emergency experienced by the world during the COVID-19 pandemic.

It is worth highlighting that no previous studies bring together these elements of structuring and restructuring during the pandemic and that the reorganization of ICUs was a necessary action to achieve assistance.

Therefore, this study aimed to identify the elements related to structuring and restructuring ICU's HR, MR, and organization/structurE processes during the COVID-19 pandemic.

METHODS

Study design

A systematic literature review was carried out in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P)[6] and the JBI[7] methodological conduct guidelines. This review was submitted to the International Prospective Register of Systematic Reviews (PROSPERO), under approved Opinion CRD42022311926.

Research question

Coppola's (1999)[5] definitions were used as a reference to elaborate on the guiding research question, adopting the definitions of HR, MR, and organization/structure processes. The research question was formulated according to the PCC strategy (Population, Concept, and Context) (XX): P: ICU; C: elements relating to the structuring and restructuring of HR, MR and organization/structure processes; C: COVID-19 pandemic. Thus, the research question of this review was: what are the elements related to the structuring and restructuring of HR, MR, and organization/structure processes carried out in ICU during the COVID-19 pandemic?

Article search and selection strategy

The search was carried out in June 2022 and updated in 2022. The MEDLINE, PubMed, Scopus, Web of Science, and Embase databases were used. The MeSH (Medical Subject Headings) and Emtree (Embase Sub-

Table 1. Syntax of the search strategy in the databases, Ceará, Brazil, 2023.

Databases	Search Strategy	References (N)
MEDLINE	("Intensive Care Units") AND (COVID-19 OR SARS-CoV-2) AND ("Hospital Restructuring")	8
	("Unidades de Terapia Intensiva") AND (COVID-19 OR SARS-CoV-2) AND ("Reestruturação Hospitalar")	3
	("Unidades de Cuidados Intensivos" AND (COVID-19 OR SARS-CoV-2) AND ("Restructuration Hospitalière")	0
PubMed	("Intensive Care Units"[All Fields] OR "ICU Intensive Care Units"[All Fields] OR "Unit, Intensive Care"[All Fields] OR "Intensive Care Unit"[All Fields]) AND ("COVID-19"[All Fields] OR "SARS-CoV-2 Infection[All Fields]" OR "Infection, SARS-CoV-2"[All Fields]) AND ("Hospital Restructuring"[All Fields] OR " Restructuring, Hospital"[All Fields] OR "Hospital Restructurings"[All Fields] OR "Restructurings, Hospital"[All Fields] OR "Reorganization, Hospital"[All Fields] OR "Hospital Reorganizations"[All Fields] OR "Reorganizations, Hospital"[All Fields] OR "Hospital Reorganization"[All Fields] OR "Hospital Diversification"[All Fields] OR "Diversification, Hospital"[All Fields])	8
Scopus	(("Intensive Care Units" OR "ICU Intensive Care Units" OR "Unit, Intensive Care" OR "Intensive Care Unit") AND (COVID-19 OR SARS-CoV-2) AND ("Hospital Restructuring" OR "Restructuring, Hospital" OR "Hospital Restructurings" OR "Restructurings, Hospital" OR "Reorganization, Hospital" OR "Hospital Reorganizations" OR "Reorganizations, Hospital" OR "Hospital Reorganization" OR "Hospital Diversification" OR "Diversification, Hospital"))	10
Web of Science	(("Intensive Care Units" OR "ICU Intensive Care Units" OR "Unit, Intensive Care" OR "Intensive Care Unit") AND ("COVID-19" OR "SARS-CoV-2 Infection" OR "Infection, SARS-CoV-2" OR "SARS CoV 2 Infection" OR "SARS-CoV-2 Infections" OR "2019 Novel Coronavirus Disease" OR "2019 Novel Coronavirus Infection" OR "2019-nCoV Disease" OR "2019 nCoV Disease" OR "2019-nCoV Diseases" OR "Disease, 2019-nCoV" OR "COVID-19 Virus Infection" OR "COVID 19 Virus Infection" OR "COVID-19 Virus Infections" OR "Infection, COVID-19 Virus" OR "Virus Infection, COVID-19" OR "Coronavirus Disease 2019" OR "Disease 2019, Coronavirus" OR "Coronavirus Disease-19" OR "Coronavirus Disease 19" OR "Severe Acute Respiratory Syndrome Coronavirus 2 Infection" OR "SARS Coronavirus 2 Infection" OR "COVID-19 Virus Disease" OR "COVID 19 Virus Disease" OR "COVID-19 Virus Diseases" OR "Disease, COVID-19 Virus" OR "Virus Disease, COVID-19" OR "2019-nCoV Infection" OR "2019 nCoV Infection" OR "2019-nCoV Infections" OR "Infection, 2019-nCoV" OR "COVID19" OR "COVID-19 Pandemic" OR "COVID 19 Pandemic" OR "Pandemic, COVID-19" OR "COVID-19 Pandemics") AND ("Hospital Restructuring" OR " Restructuring, Hospital" OR "Hospital Restructurings" OR "Restructurings, Hospital" OR "Reorganization, Hospital" OR "Hospital Reorganizations" OR "Reorganizations, Hospital" OR "Hospital Reorganization" OR "Hospital Diversification" OR "Diversification, Hospital"))	3
Embase	('intensive care units' OR 'ICU intensive care units' OR 'unit, intensive care' OR 'intensive care unit') AND ('covid-19' OR 'sars-cov-2 infection' OR 'infection, sars-cov-2' OR 'sars cov 2 infection' OR 'sars-cov-2 infections' OR '2019 novel coronavirus disease' OR '2019 novel coronavirus infection' OR '2019-ncov disease' OR '2019 ncov disease' OR '2019-ncov diseases' OR 'disease, 2019-ncov' OR 'covid-19 virus infection' OR 'covid 19 virus infection' OR 'covid-19 virus infections' OR 'Infection, covid-19 virus' OR 'virus infection, covid-19' OR 'coronavirus disease 2019' OR 'disease 2019, coronavirus' OR 'coronavirus disease-19' OR 'coronavirus disease 19' OR 'severe acute respiratory syndrome coronavirus 2 infection' OR 'SARS coronavirus 2 infection' OR 'covid-19 virus disease' OR 'covid 19 virus disease' OR 'covid-19 virus diseases' OR 'disease, covid-19 virus' OR 'virus disease, covid-19' OR '2019-ncov infection' OR '2019 ncov infection' OR '2019-ncov infections' OR 'infection, 2019-ncov" or "covid19' OR 'covid-19 pandemic' OR 'covid 19 pandemic' OR 'pandemic, covid-19' OR 'covid-19 pandemics') AND ('hospital restructuring' OR 'restructuring, hospital' OR 'hospital restructurings' OR 'restructurings, hospital' OR 'reorganization, hospital' OR 'hospital reorganizations' OR 'reorganizations, hospital' OR 'hospital reorganization' OR 'hospital diversification' OR 'diversification, hospital')	139
Total		171

ject Headings) terms were used to select the controlled descriptors associated with the research question. The descriptors were associated with the Boolean operators "AND" and "OR," and parentheses and designations of the descriptors were also used to ensure a topic-sensitive search strategy (Table 1).

Inclusion and exclusion criteria

Studies with data on the structuring and restructuring of ICUs in terms of HR, MR, and organization/structure processes during the COVID-19 pandemic, published between 2019 and 2022 (justifying the time restriction by the discovery of the SARS-CoV-2 virus in 2019), records in English, Portuguese, and Spanish, available in full text, and published as original articles, were included. Review articles, commentaries, letters to the editor and non-peer-reviewed articles (in press) were excluded.

Study categorization

Studies containing information on the structuring and restructuring of ICU during the COVID-19 pandemic that dealt with HR, MR and organization/structure processes carried out in the units were considered eligible.

There was a time cut of articles published between 2019 and 2022, justified by the discovery of the SARS-CoV-2 virus that occurred in 2019.

Study selection

The references were exported to the Rayyan software. Studies were analyzed independently, based on the inclusion and exclusion criteria. Regarding divergences in assessing titles and abstracts, these were resolved by consensus at a subsequent meeting. Ultimately, the eligible preliminary studies had their full texts assessed independently and double-blindly by two reviewers, seeking to meet the eligibility criteria. The divergences found were resolved by consensus in a second meeting. Excluded studies were registered in a separate database, explaining the reasons for exclusion.

Data collect

After selecting the studies, they were analyzed by two unblinded reviewers, and categorization information was extracted from studies (article, author/year, journal, country and title), which is shown in Table 2 of the results section. The data extracted allowed us to understand the specificities of the populations, context, geographical location, study methods and phenomena of interest relevant to the review question and specific objectives. With regard to the elements related to the research question, related to the aspects defined by Coppola,[5] Table 3 was presented (article, HR, MR and organization/structure processes). Any disagreement among reviewers was resolved through discussion of the findings.

Risk of bias

The risk of bias was assessed by two authors independently, using tools recommended for qualitative studies.[7] The risk of bias was considered high when the study obtained 49% "yes" answers, moderate, when the study obtained 50% to 69% "yes" answers, and low, when the study reached more than 70% "yes".[9]

Data analysis

The results presented in the articles covering HR, MR and organization/structure processes were transcribed and prepared into a text *corpus* for lexicographic textual analysis, using the software *Interface de R pour les Analyses Multidimensionnelles de Textes et de Questionnaires* (IRaMuTeQ). IRaMuTeQ is a free open-source software created by Pierre Ratinaud, in 2009, with GNU GPL(v2) license, which allows the statistical analysis of the text *corpus*.[10] Two researchers interpreted the data that resulted from the analysis.

Similarity analysis in IRaMuTeQ is a technique that identifies and graphically represents the relationships among words based on the frequency of their co-occurrences in a text. This analysis constructs a network where words are the nodes and the connections among them reflect the frequency with which they appear together in a specific context window, revealing the text's structure and highlighting the main themes. It helps to visualize the semantic proximity and the relative importance of words within the analyzed *corpus*.[10]

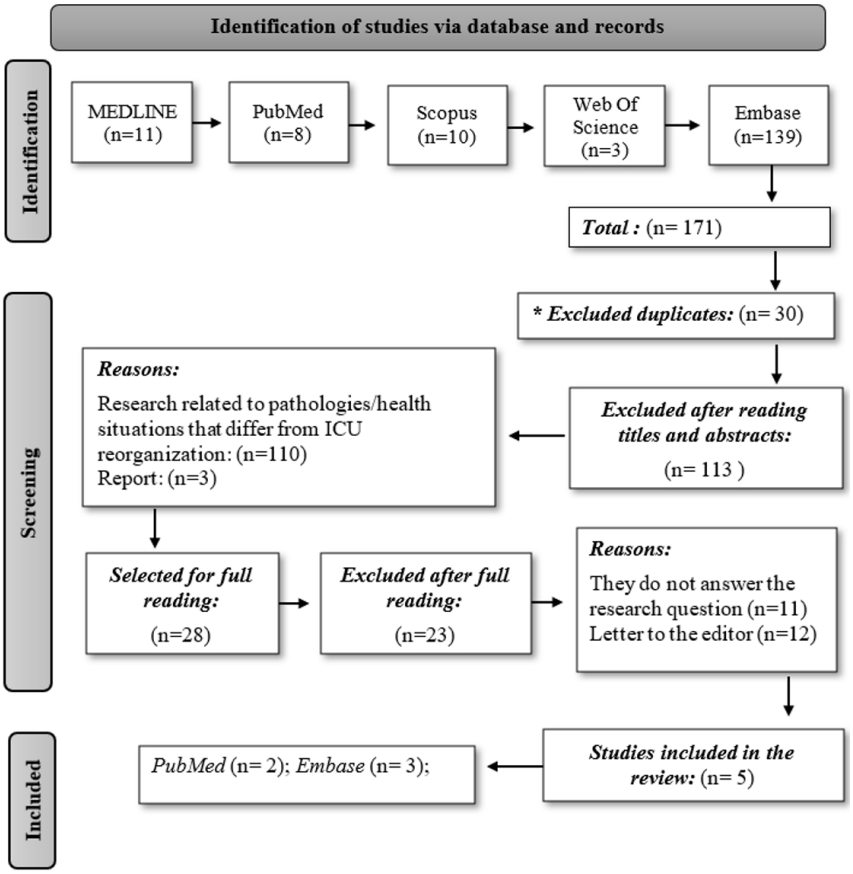
Therefore, this method involved *corpus* preparation, including text collection, cleaning, and normalization. Subsequently, the texts were tokenized and segmented for co-occurrence analysis, which was calculated, resulting in a matrix that represents how often the words appeared together in a defined context window. Based on these co-occurrences, similarity measures such as the Jaccard coefficient or Euclidean distance were calculated to quantify the semantic proximity among words. The similarity network was then constructed, where words are nodes and their connections reflect the strength of the co-occurrences.

RESULTS

During the first phase of study selection, 171 articles were found, with 30 articles duplicates were excluded, and 113 articles were analyzed by title and abstract, of which 110 were research related to pathologies/health situations that differ from ICU reorganization, and three were reports and were excluded from the study. Twenty-eight were selected for full reading; 11 did not answer the research question, i.e. did not contain elements of ICU restructuring; and 12 were letters to the editor, leaving five studies selected for qualitative analysis (Figure 1).

Characteristics of eligible studies

Most of studies were published in 2021[12,4,13], mainly in Spain[13,14] and mostly indexed in Embase, in different journals. Regarding the identification of resources related to the reorganization of ICUs, the five studies showed significant responses within the definitions of resources described by Coppola.[5]



**Exclusion done by Rayyan revision manager.*

Figure 1. PRISMA flow diagram, which describes the process of searching, identifying, including and excluding articles.

Table 2. Study characterization, Brazil, 2023.

Article	Author/year	Country	Title
2	Borel et al. 2021	France	Transformation of a hospital restaurant into an orientation intensive care unit
5	Nunez-Villaveiran et al. 2020	Spain	All for One and One for All: Voluntary Physicians in the Intensive Medicine Units During the COVID-19 Outbreak in Spain
1	Shaparin et al. 2021	United States	Adaptation and restructuring of an academic anesthesiology department during the COVID-19 pandemic in New York City: Challenges and lessons learned
3	Singh et al. 2021	India	Challenges faced in establishing a dedicated 250 bed COVID-19 intensive care unit in a temporary structure
4	Vilallonga et al. 2020	Spain	Transforming a surgical department during the outbreak of new coronavirus pandemic. Clinical implications

Risk of individual studies bias

As for methodological quality, most studies were categorized as having high methodological quality[10]. Of the five articles included[4,11,13], four had 80% positive instrument assessments, and only one had 70%.

Data analysis

Similarity analysis led to the composition of six core words, represented by the words COVID-19, patient, care, bed, ICU, and equipment. The branching among the six cores reveals how the terms are strongly interconnected and convey the notion of the aspects of resource management during the COVID-19 pandemic.

The word COVID-19 presented as central, concerns the pandemic moment, strongly linked to the word patient. The word equipment covers two cores, with important terms in the restructuring process, linking the importance of protection and the use of PPE as well as intubation and the teamwork process in intensive care. Another analysis considered is the connection of the words bed, ICU and increase, which are aspects observed in all studies as the purpose of administration and increasing beds to meet the great demand of the pandemic. The branch to the nucleus encompassing the word care presents links that direct quality assistance and strengthen this action.

Table 3. Extraction of what refers to human resources, material resources and organization/structure processes, Brazil, 2023.

Article	Human resources	Material resources	Material resources
1	**For professionals:** Train and promote leadership for those with recent ICU experience; provide up-to-date education on equipment decontamination and use of protective equipment; increase staff well-being to deal with increased demand and foster resilience for future increases. **For patients:** Recruitment of employees from the anesthesiology department for COVID-19 ICUs, enabling better assistance; selection of COVID-19 patients based on severity depending on facility capabilities; filter and disseminate relevant, high--quality information related to COVID-19.	Plan the adequate supply of personal protective equipment (PPE); existing oxygen supply was equipped to serve 1,200 patients; availability of various medications; promptly guarantee equipment such as anesthesia circuit filters, intubation boxes and other airway management equipment.	Organization/structure processes Ensuring ICU beds dedicated to the care of positive or unknown patients for COVID-19; 16-room stand-alone outpatient surgery center that has been converted into a COVID-19 ICU inpatient facility and 60 beds on the floor.
2	**For professionals:** Due to the need for a long working day, the unit's structure allowed each person to adapt as quickly as possible to a new environment, through local signs; operational care teams for disease prevention; the presence of psychologists. **For patients:** Provide safe care in terms of quality of care; all medical, paramedical and administrative procedures have been written down and standardized as much as possible.	The restructuring process required an adaptation of the facilities to supply medical needs and lighting equipment; creation of an oxygen plant; all beds were equipped with a standardized respirator, a multiparameter monitor and four electric syringe pumps; rapid diagnostic equipment for COVID-19; portable X-ray machine and an ultrasound machine; equipment for difficult intubation; intubation kits containing video laryngoscope, videolaryngoscopy blades, intubation probe, cold light laryngoscope, blades nº 3 and 4, Guedel cannula nº 2, 20 ml syringe, clamp, plaster roll, PFF2 mask + glasses.	All medical, paramedical and administrative procedures have been written down and standardized as much as possible; in order to facilitate the location of personnel, the locations were color--coded and a care cart was set up for each group of four patients. There was the transformation of a hospital restaurant into a unit with 43 beds for critical care for patients with COVID-19.
3	**For professionals:** All healthcare workers wearing full PPE; reasonably acclimatized environment for work. **For patients:** Indoor environment with climate control; infection control team.	The adhesion of the most adequate number of critical equipment available in a short period of time; medications and laboratory objects; electricity and air conditioning; in addition to powering the generator, nasal cannulas, infusion pumps and patient monitors would continue to function even in the event of a power failure; measures to reduce noise levels inside the ICU, moving noise-generating machinery away from the patient care area and the use of barriers; the ICU water supply was provided by sources; disinfection and correct disposal of biomedical waste.	Construction of a 25,000 square meter temporary hospital with 250 ICU beds, created to increase COVID-19 care ICU beds in the city by 11%.
4	**For professionals:** 90% of professionals were trained to deal with matters related to COVID-19; control of the physical and emotional overload of professionals; use of PPE; physicians from different specialties (surgical and non-surgical) were reassigned to work in multidisciplinary teams led by infectious disease specialists, internal medicine or pulmonology. **For patients:** Decreased waiting time for the ICU; patient safety protocols; protect patients with and without COVID-19 from staff and vice versa.	Improvement in the quality of instruments and equipment to meet the needs of new beds;	In addition to the 103 ICU beds, 120 new beds were created to meet the high demand of patients with COVID-19; reformulation of hospital wards, decrease in the number of surgical procedures and increase in ICU beds.
5	**For professionals:** Non-critical care staff would benefit from basic adult critical care courses; strategies such as health worker education, provision of adequate PPE, availability of adequate treatment (or prophylaxis) for various hazardous agents, and ensuring infection control. **For patients:** Critical care staff has been expanded with non-critical care physicians working as "force multipliers", intensivists and critical care nurses.	Need to acquire new equipment, such as equipment for diagnosing COVID-19, new ultrasound and portable X-ray devices.	Research with doctors from 17 regions of Spain, totaling 258 ICUs studied, in which the capacity of ICU beds during the pandemic outbreak increased by 160%.

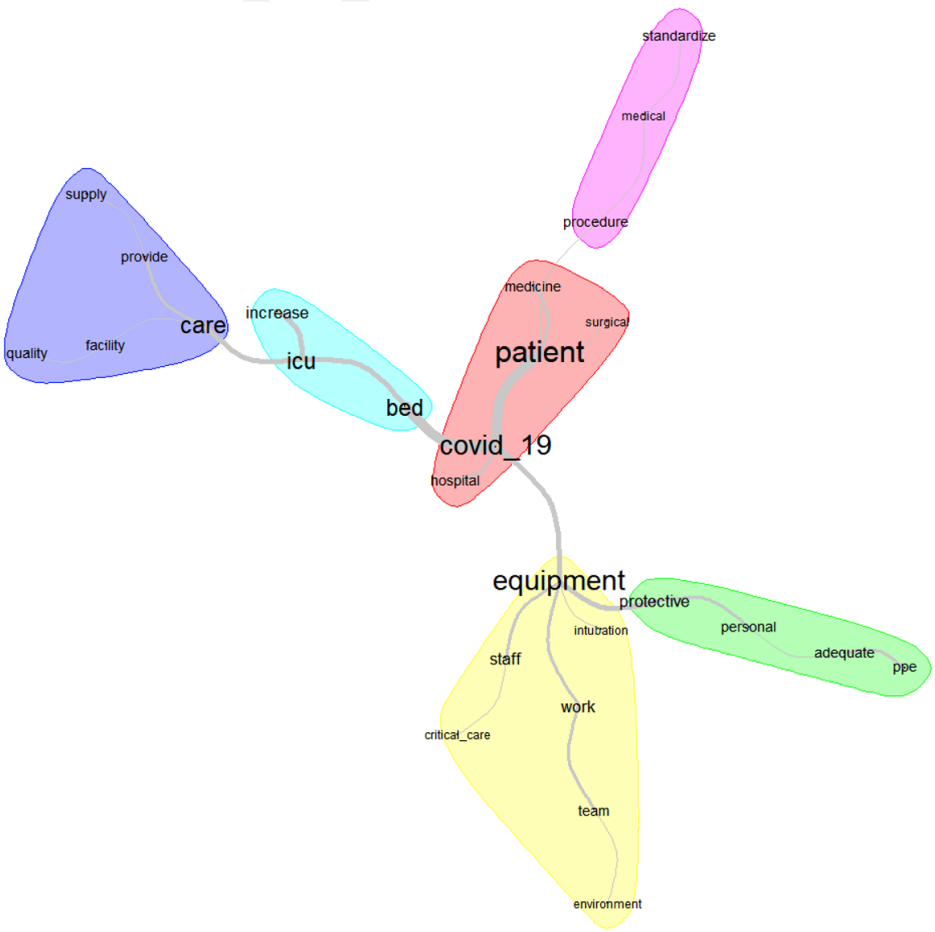


Figure 2. Similarity analysis tree among words from the text corpus, Brazil, 2023.

DISCUSSION

During the COVID-19 pandemic, HR in health systems were impacted. Studies report losses in the mental health of professionals working on the front line related to the high flow of work, exhausting routine, impaired sleep, stress in work settings, among other factors.[14] In the restructuring process, managers were concerned about developing actions that would minimize damage to professionals' mental health, such as psychological care, hiring more professionals, overload control, and an air-conditioned environment.[4,11,14]

The correct use of PPE is an action to prevent the spread and contagion of the SARS-CoV-2 virus and should be encouraged throughout work settings, especially for professionals who work on the front line in ICUs.[15] The availability of this equipment must be carried out by hospital units as well as the implementation of protocols for its use.[11,12]

Training professionals for ICU care was mentioned by Shaparin *et al.*[12] as a necessary activity, but the author makes it clear that there was no large-scale training, due to the high demand of patients in need of care, but to assist in this process, those who had expertise in critical care played a role of leadership in the units. This action is a strategy to avoid the occurrence of errors in practice or handling of some equipment, and consequently, provides patient safety.[13]

To meet hospitals' demands and needs, prioritization scales were carried out, from the most severe to the least severe care.[11,13] In the COVID-19 scenario, severity protocols helped in the flow of care, providing critical patients with the immediate intervention compared to those who were not so serious. This action also made it possible to reduce the burden on ICU professionals.[16]

For Do Prado *et al.*,[17] worker safety is considered part of patient safety, since adequate resources, prepared professionals, a favorable environment, and administrative protocols show improvement, both in the development of care and in patient health outcomes.

MR guarantee in ICUs enables the proper functioning and provision of quality service, since, to provide care to critically ill patients, there is a need for demand for adequate materials, ensuring the supply of all areas of restructuring, preventing the service suffers interruptions that are harmful to professionals and patients.[18] This resource is directly linked to the particularities of HR so that material, logistics, and supplies can be managed, and it is necessary to have good functioning to meet patients' and professionals' interests.[19]

Professional protection through the reduction of risk exposure in work settings is a guarantee of quality care.[20] Therefore, when it comes to the availability of PPE, there are reported difficulties in ensuring the maintenance of this equipment, especially personal protective

masks.[11] After the guidance of the World Health Organization on the use of masks by the general population, to contain the infection by the virus that causes COVID-19,[21] there was a collapse in the distribution of these materials, causing an overload in the supplying companies and lack in hospitals. However, the guarantee of use by professionals was reported in most studies.[11,12,14]

In ICU, oxygen therapy makes it possible to maintain the body's metabolic balance, improve tissue and organ oxygenation, correct hypoxemia, and plays a fundamental role for patients with airway infections.[22] This resource proved to be of great value in ICUs.[23] Some of those presented in this review developed the creation of their oxygen plants and ensured the supply of this resource throughout the pandemic.[4,13] To supply oxygen, auxiliary materials are needed, such as multiparameter monitors, laryngoscope, laryngoscopy blades, intubation probe, cold light laryngoscope, blades nº 3 and 4, Guedel cannula, 20 ml syringe, clip, high flow, face masks and glasses.[4]

Electricity is a resource present in ICUs that cannot be scarce, since the operation of the entire care process requires electricity, as for the use of monitoring equipment, lung fans, defibrillators, lighting, and air conditioning of the environment was maintained through generators for ICU maintenance.[12,13]

MR security in the restructuring process aims to optimize professional work, ensuring more accurate monitoring of patients and progress in clinical results. This process of maintaining materials must be assessed by managers to maintain the perpetuation of instruments with the profile of this care ward.[22]

This method revealed sectoral bureaucratic-administrative resources, which made up the process of structuring and restructuring the units. The main objective is to detail changes or the creation of new sectors resulting from the COVID-19 pandemic. The guarantee of adequate beds for the care of critically ill patients, either through the expansion of existing hospital units or the development of new emergency units.

Shaparin *et al*.[12] reported a 16-room sector shift from a surgical and anesthesiology wing to a 60-bed ICU COVID-19 unit in New York. The authors stated that the restructuring process was successful, and point to safety and commitment to well-being, preserving the quality of patient care. This process also made it possible to maximize professionals' experience and effective communication. Even during the subsequent waves of COVID-19, the hospital maintained subspecialty availability for emergency procedures in operating rooms.

Similar aspects were observed in the study by Borel *et al*.[4] However, the changes took place in a hospital restaurant for employees, which was transformed into a 43-bed wing for critical care of COVID-19 patients in Paris. For this, engineers and doctors guided the implementation of this reform, which took place in 15 days.

In mid-2020, shortly after the pandemic was declared, in New Delhi, construction began on a hospital center with a temporary ICU of 25,000 square meters, with 250 beds. Sing *et al*.[13] stated that the unit had a high structural level. The ICU was integrated in an accessible way to other wards of the hospital, allowing access to the wards, which were occupied by patients who were discharged from the ICUs. The entire restructuring process took place in 15 days, similar in time to the project by Borel *et al*.[4]

Due to the reduction in the performance of elective surgeries in a tertiary hospital in Spain, its surgical wards were transformed into ICUs for patients with COVID-19. Vilallonga *et al*.[13] reported the needs analysis process with the increased demand for critical care and the exhaustion of the 103 existing beds. The decrease in surgeries made it possible to create 120 new beds for high demand. The authors reported that this action avoided the increase in mortality rates, optimizing the surgical space as much as possible.

In this scenario, there was a great capacity for expansion in ICU beds in Spain. Nunez-Villaveiran *et al*.[14] reported a 160% increase in beds in different hospital units resulting from COVID-19 infection. These actions are part of the human disaster prevention plan, as intensive care resources have been increased to accommodate large numbers of critically ill patients.

The limitation of this review is identified by the specificity of the subject and consequent reduced production on the topic. Moreover, we limited the language of the studies and only included studies available online. However, an exhaustive analysis of the elements identified was carried out, which improved the results.

The study could serve as a guide for managers and healthcare professionals to understand the process of reorganizing ICUs, aimed at caring for patients with COVID-19.

CONCLUSION

The main elements necessary for structuring and restructuring ICU to meet the pandemic scenario demands are HR: professional training to care for patients with COVID-19 and correct use of PPE, an increase in the number of healthcare professionals, an increase in strategies for team and patient well-being, relocation of professionals among care sectors, presence of psychologists in services to assist professionals and greater adherence to the use of PPE; MR: increased supply of adequate PPE, increased supply of oxygen, increased supply of medications and increased need for equipment such as anesthesia circuit filters, mechanical ventilators, intubation boxes and other equipment for airway management; and organization/structure processes: increased demand for hospitalization beds, including ICU, and adaptation of facilities for COVID-19 hospitalization sectors.

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AUTHORS' CONTRIBUTIONS

Luis Fernando Reis Macedo: contributed to the literature search, writing the introduction, methodology, discussion, preparation of tables. **Kenya Waléria de Siqueira Coelho Lisboa:** contributed to the project administration, interpretation and description of results, conclusions, and review. **Thais Rodrigues de Albuquerque** contributed to the writing of the abstract, methodology, interpretation of results, conclusions, review, and statistics. **Alexandre Pazetto Balsanelli** contributed to the critical review of the study, analysis, and validation of data. **Sarah De Lima Pinto** contributed to the project administration, literature search, and critical review. **Izabel Cristina Santiago Lemos de Beltrão** contributed to the project administration, literature search, writing the abstract, and statistics. **Gyllyandeson de Araujo Delmondes** contributed to the project administration, data analysis, and critical review of the text.

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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Revista de Epidemiologia e Controle de Infecção

Hospital Santa Cruz

REVIEW ARTICLE

Hospital Epidemiology Units in Brazil: an integrative literature review

Núcleos Hospitalares de Epidemiologia no Brasil: uma revisão integrativa de literatura

Unidades de Epidemiología Hospitalaria en Brasil: una revisión integradora de la literatura

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Corresponding Author:
Rodrigo Faria Dornelas
rodrigodornelas11@hotmail.com

Address: R. 235, s/n - Setor Leste Universitário, Goiânia, Goiás, CEP 74605-050.

Rodrigo Faria Dornelas[1];
Ana Luiza Lima Sousa[1];

[1] *Universidade Federal de Goiás, Goiânia, Goiás, Brazil.*

ABSTRACT

Background and Objectives: the activities of epidemiological surveillance within hospital settings assume diverse structures and work processes according to different regions. This study aimed to map the studies conducted on the structure and/or processes of Hospital Epidemiology Units in Brazil. **Methods**: this is an integrative literature review conducted in the PubMed, Virtual Health Library (VHL), Brazilian Digital Library of Theses and Dissertations (BDTD), and CAPES Journals databases, using predefined descriptors. The search covered the period from 1971 to 2022. The construction of this study was guided by checklist items and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis elaboration. The process of selecting and organizing study inclusion and exclusion was carried out through the Rayyan application. **Results:** eighteen studies were identified using controlled descriptors (Epidemiologic Surveillance Services; Hospitals; and Health Evaluation) in the selected databases, distributed across ten federal units. Regarding the searches for studies on Hospital Epidemiology Units, we came across studies on other subjects that do not necessarily provide information on the functioning or systematic nature of the organization. These studies present as their object, for instance, the illnesses reported by the unit. **Conclusion:** it was identified that the studies address topics such as notification and investigation of diseases and injuries, and active search. Some even verticalize analyses on integration between sectors within hospital settings and in the external care network. However, there are few studies that analyze the performance of the units – analysis of processes and outcomes.

Keywords*: Epidemiology. Epidemiological Surveillance Services. Hospitals. Health Assessment. Hospital Epidemiology Unit.*

RESUMO

Justificativa e Objetivos: as atividades de vigilância epidemiológica dentro de ambientes hospitalares assumem estruturas e processos de trabalho diversificados segundo as diferentes regiões. Este estudo teve como objetivo mapear os estudos realizados sobre estrutura e/ou processos dos Núcleos Hospitalares de Epidemiologia no

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Brasil. **Método**: trata-se de revisão integrativa da literatura realizada nas bases de dados PubMed, Biblioteca Virtual em Saúde (BVS), Biblioteca Digital Brasileira de Teses e Dissertações (BDTD) e Periódicos CAPES, usando descritores pré-definidos. A busca compreendeu o período de 1971 a 2022. A construção deste estudo foi guiada pelos itens de checagem e elaboração do *Preferred Reporting Items for Systematic Reviews and Meta-Analysis*. O processo de seleção e organização da inclusão e exclusão das publicações foi realizado por meio do aplicativo Rayyan. **Resultados**: foram identificados 18 estudos, utilizando-se descritores controlados (*Epidemiologic Surveillance Services; Hospitals; Health Evaluation*) nas bases de dados selecionadas, distribuídos em dez Unidades Federativas. Em relação às buscas por publicações sobre os Núcleos Hospitalares de Epidemiologia, deparamo-nos com estudos sobre outros assuntos que não necessariamente informam sobre o funcionamento ou sistemática de organização. Estes apresentam como objeto, por exemplo, os agravos notificados pelo núcleo. **Conclusão**: foi identificado que os estudos abordam temas como notificação e investigação de doenças e agravo, e busca ativa. Alguns ainda verticalizam análises sobre integração entre setores dentro do ambiente hospitalar e na rede de assistência externa. No entanto, são escassos estudos que analisassem a atuação dos núcleos – análise de processos e resultados.

***Descritores**: Epidemiologia. Serviços de Vigilância Epidemiológica. Hospitais. Avaliação em Saúde. Núcleo Hospitalar de Epidemiologia.*

RESUMEN

Justificación y Objetivos: las actividades de vigilancia epidemiológica en entornos hospitalarios asumen estructuras y procesos de trabajo diversos según las diferentes regiones. Este estudio tuvo como objetivo mapear los estudios realizados sobre la estructura y/o procesos de los Núcleos de Epidemiología Hospitalaria en Brasil. **Métodos**: se trata de una revisión integrativa de la literatura realizada en las bases de datos PubMed, Biblioteca Virtual en Salud (BVS), Biblioteca Digital Brasileña de Tesis y Disertaciones (BDTD) y Periódicos CAPES, utilizando descriptores predefinidos. La búsqueda abarcó el período de 1971 a 2022. La construcción de este estudio fue guiada por los elementos de verificación y elaboración del *Preferred Reporting Items for Systematic Reviews and Meta-Analysis*. El proceso de selección y organización de la inclusión y exclusión de las publicaciones se llevó a cabo a través de la aplicación Rayyan. **Resultados**: se identificaron 18 estudios utilizando los descriptores controlados (*Epidemiologic Surveillance Services; Hospitals; Health Evaluation*) en las bases de datos seleccionadas, distribuidos en diez Unidades Federativas. En relación a las búsquedas de publicaciones sobre Centros Hospitalarios de Epidemiología, encontramos estudios sobre otros temas que no necesariamente aportan información sobre el funcionamiento o la sistemática de la organización. Estos presentan como objeto, por ejemplo, los problemas notificados por el núcleo. **Conclusión:** se identificó que los estudios abordan temas como notificación e investigación de enfermedades y lesiones, y búsqueda activa. Algunos incluso verticalizan los análisis sobre la integración entre sectores del entorno hospitalario y la red asistencial externa. Sin embargo, son pocos los estudios que analizan el desempeño de los centros – análisis de procesos y resultados.

***Palabras Clave**: Epidemiología. Servicios de Vigilancia Epidemiológica. Hospitales. Evaluación de la Salud. Núcleo Hospitalario de Epidemiología.*

INTRODUCTION

Epidemiological surveillance has a history dating back to the 19th century, and was limited to data collection, compilation, assessment and dissemination to health authorities and the general public, with the main objective of early detection of patients with a view to their isolation.[1]

The expansion of epidemiological surveillance actions to the hospital level began with Ordinance 2,529 of November 2004, which created the Brazilian National Subsystem of Epidemiological Surveillance in hospital settings and, thus, paved the way for implementing Hospital Epidemiology Units (HEU) as a way of optimizing health surveillance actions from the hospital context, with elements already inherent to epidemiological surveillance, including data collection and processing activities, data analysis and interpretation, recommendation of prevention and control measures, promotion of prevention and control actions, assessment of the effectiveness of the measures adopted and dissemination of relevant information.[2,3,4]

In 2010, through Ordinance MoH/MO 2,254 of August 5, 2010, Hospital Epidemiological Surveillance (HES) was established within the Brazilian National Health Surveillance System (SNVS - *Sistema Nacional de Vigilância em Saúde*). Its purpose was to define an initial network of national reference hospitals for developing epidemiological surveillance actions in hospital settings.[3]

HEU are structures created to carry out epidemiological surveillance in hospitals and health units. The main objective of these units is to ensure the development of epidemiological surveillance activities in hospital health settings, preventing and controlling diseases, health problems and events (DHE) and other hospital infections. They are made up of healthcare professionals with ex-

perience and/or training in public health who work in an articulated manner, aiming to detect, report and investigate illnesses, in close coordination with the Brazilian National Public Health Emergency Alert and Response Network (CIEVS Network) as well as the detection of deaths of women of childbearing age, declared maternal deaths, infant and fetal deaths, deaths from infectious diseases and from ill-defined causes. Thus, they carry out activities such as data collection and analysis, DHE and infection outbreak identification, prevention measure implementation and suspected case investigation.[5]

The activities developed by HEU, within hospital settings, assume structures and work processes guided by guiding ordinances to be developed. Every unit should act by reporting and investigating diseases and injuries through active search, data consolidation, analysis and dissemination of information, promotion of control actions, in addition to assessment of the efficacy and effectiveness of the measures adopted, promotion of integration between key sectors of the hospital and timely monitoring.[6-7]

It is important to understand HEU, demonstrating their performance within hospital units and how their production can reflect on local managers' decision-making and on the knowledge of emerging diseases faster and accurately.

This work aims to map the studies carried out on the structure and/or processes of HEU in Brazil. Carrying out an integrative review on the topic can help identify situations within the units with their connections and divergences.

MÉTODOS

This is an integrative literature review to map studies on HEU. The types of studies included in the study were full articles published in indexed journals, dissertations and theses. The search period considered was from 1971 to 2022, filtered in the PubMed, Virtual Health Library (VHL), Brazilian Digital Library of Theses and Dissertations (BDTD) and CAPES Journals (CAFe access) databases, using defined strategies, according to Chart 1. The filters used in the databases to search for descriptors were the title or, in the abstract, the descriptors indexed in the aforementioned databases. The studies were exported on December 21, 2022.

The construction of this study was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA 2020) checking and preparation items, aiming to increase the quality and reliability of the information obtained.

Studies that assessed the structure and/or processes and/or outcomes of HEU in Brazil were included. Therefore, articles that studied communicable and non-communicable diseases and injuries, hospital infections and other situations that do not constitute HEU structuring were excluded.

The categorization of studies available in the databases used in the study was carried out by a researcher with experience in HES, using the online platform Rayyan.

The following DeCS terms were used with the combined search strategies and the Boolean operators OR and AND (Chart 1):

The descriptors used in the BDTD platform were inserted in Brazilian Portuguese, as this was more successful in locating available studies.

The process of selecting and organizing the inclusion and exclusion of articles was carried out using Rayyan application, where titles and abstracts were read, duplicates were excluded, the reasons for exclusion were categorized, and the articles were selected for full reading.

An Excel spreadsheet was created to extract data from articles selected for full reading with the following variables: study title; authors; journal name and year of publication; study period; study location; study focus (structure, process or outcome); objective; and study considerations.

Chart 1. Method for searching journals in databases with controlled descriptors.

METHOD			
Database	**Controlled descriptors**	**Search strategy**	**Studies retrieved (N)**
PubMed	Epidemiologic Surveillance Services Hospitals Health Evaluation	((Epidemiologic Surveillance Services) AND (hospitals)) AND (Health Evaluation)	353
VHL	Epidemiology/Epidemiologic Surveillance Services Hospitals	(Epidemiology) OR (Epidemiologic Surveillance Services) AND (hospitals) AND (Health Evaluation)	198
BDTD	Health Evaluation Epidemiologia/Serviços de Vigilância Epidemiológica Hospitais	All fields: Epidemiologia OR All fields: Serviços de Vigilância Epidemiológica AND (All fields: Hospitais) AND (All fields: Avaliação em Saúde)	160
CAPES JOURNALS	Avaliação em Saúde Epidemiologic Surveillance Services Hospitals Health Evaluation	Any field contains Epidemiologic Surveillance Services and any field contains Hospitals and any field contains Health Evaluation	647
Total			1,358

RESULTS AND DISCUSSION

All studies (n=1,358; 100%) found through database analysis were exported to Rayyan to exclude duplicates (n=94; 6.92%). After reading the title and abstract, another 1,099 (80.93%) were excluded because they did not match the study objective. Others (n=06, 0.44%) were excluded because they were not available for reading in full. And 159 (11.71%) articles remained for full reading, as shown in Table 1.

After reading the selected articles in full (n=159), we excluded 152 because they were not consistent with the proposed objective. In order to meet the study objective, seven studies were included (Table 1).

We listed the reasons for exclusion of articles after reading titles and abstracts, as observed in the PRISMA flow diagram (Chart 2). We verified studies that had as their research object diseases, injuries and events in public health, and chronic non-communicable illnesses accounted for n=462 (42.2%) of reasons for exclusion.

Table 1. Refinement of analysis performed after exporting articles to the databases.

Result of automated analysis by Rayyan application	Number of studies
Total studies	1,358
Studies excluded due to duplication	94
Studies excluded due to articles not being available in full	06
Studies excluded after reading titles and abstracts	1,099
Studies excluded after reading full text	136
Studies excluded because they do not address Hospital Epidemiological Surveillance (international scenario)	16
Studies included	07

Source: prepared by the author (2023).

In order to identify studies through other methods and further refine the search, the bibliographic references of the seven studies included in database analysis were checked. Thus, we identified 923 bibliographic reference records. After analyzing these references, 11 studies that met the study objectives were eligible, as observed in the PRISMA flow diagram presented in Chart 2.

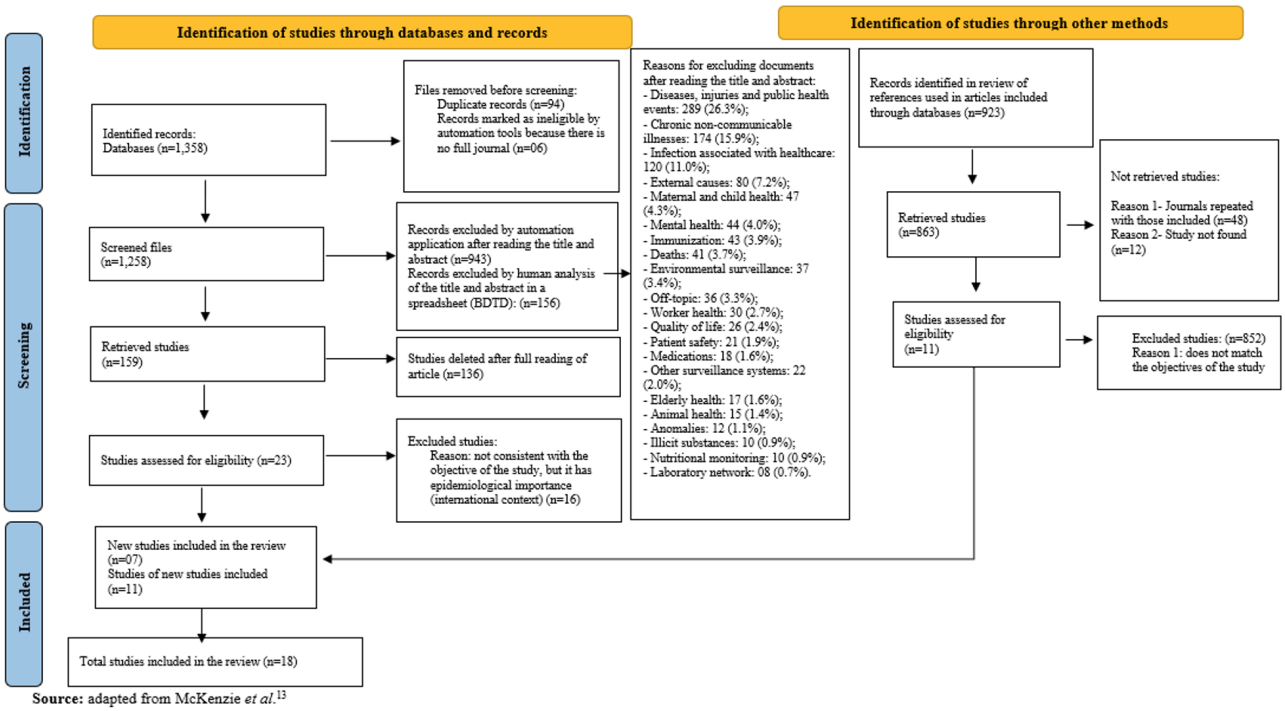
The PRISMA flow diagram shows that the number of journals reviewed in this process totaled 2,281 records. Eighteen studies were included, identified in the sum of the following search strategies: databases (n=07) and other methods (bibliographic references of articles) (n=11). As this is an integrative review, this research was not submitted to a Research Ethics Committee (REC).

In accordance with the study objectives, 18 studies were included in this integrative review (Figure 2; Chart 3), which can therefore be distributed within the Federative Units (Figure 2).

In the analysis of included studies, we found works by several authors meeting different objectives. We observed that four studies carried out in the states of Pernambuco and Piauí, assessing HEU implementation, recorded moments of progress and setbacks. Moreover, there were deficiencies in the physical and material structure, a shortage of human resources and the need for training, compromising their operationalization.[8,9,12]

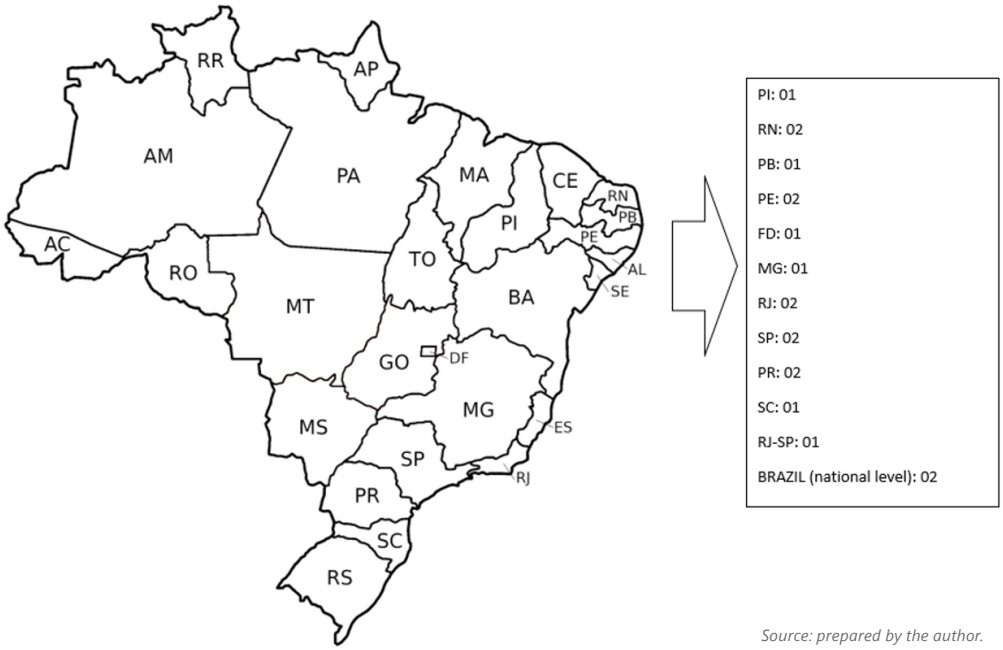
In turn, a study carried out in the state of Rio de Janeiro in 2017 reports the experience and challenges of implementing HEU. The authors describe that the unit plays a fundamental role as a reporting unit for the municipality and the state.[10]

A study conducted in Brasília in 2013 presented a situational diagnosis of the emergency hospital network's response capacity to events associated with international



Source: adapted from McKenzie *et al.*[13]

Figure 1. PRISMA 2020 flow diagram: Hospital Epidemiology Units: an integrative literature review.



Source: prepared by the author.

Figure 2. Distribution of the 18 studies included in the review at national level

travelers. The authors observed that notification flows in HEU are not consolidated among professionals and there is a dichotomy between professionals working in care and surveillance.[13,27]

Another problem detected was the accumulation of HEU activities, performing, among other functions, the active search for events in hospitals, the investigation of events in their area of coverage, the performance of activities in other sectors concurrently with HEU activities, not having agile and efficient means of communication, revealing a lack of specific training for professionals in surveillance teams and a deficiency of human resources.[13]

A study on HEU in the state of São Paulo indicated that hospital surveillance has been carried out by highly qualified professionals, given their training and experience in the area, with a predominance of nurses. Most services are coordinated by medical professionals. Active search was the predominant form of screening for cases of diseases and conditions requiring compulsory notification, and several strategies were used for this purpose. Study participants considered insufficient human resources, difficulty in raising awareness among healthcare professionals and high workload as factors that hinder work processes.[14]

Still in São Paulo, a study carried out between 2006 and 2011, assessing the HEU network, contextualizing structure, work process and outcomes, demonstrated that, from the perspective of physical infrastructure, materials and equipment, the units present favorable conditions both in relation to the adaptation of their structures and in relation to the availability of IT equipment. Most of them face significant staff shortages. There are still some units that are in the process of adapting to certain indicators and need to improve their procedures comprehensively. This involves not only organizing the activities carried out in HEU, but also expanding staff.[15]

In order to identify the relationship between the organizational climate in the HEU in the city of Natal, RN, in 2010, it was suggested that the performance of epidemiological surveillance in hospital settings demands professionals with a profile that ranges from the ability to overcome challenges to the ability to raise awareness of care professionals in the process. Furthermore, it is essential to have the necessary flexibility to deal with the transformations imposed by the environment in which the institution is located.[16]

Another study conducted in Natal on nurses' knowledge of HES actions concluded that most nurses are aware of epidemiological surveillance actions, especially notification actions, but do not notify the HEU. Most nurses, when identifying ND, do not communicate them to HEU. As a result, the information is fragmented and lost so that it does not express the performance of integrated work with this core group.[17]

Research conducted in Minas Gerais analyzed ND and injuries that occurred in a university hospital's HEU. Through detailed data analysis, it seeks to inform both the profile of the diseases reported and possible areas for improvement in the notification process and in the response to these events, thus promoting advances in public health management, contributing to implementing new HEU, reorganizing existing ones and preventing communicable diseases.[20]

A nationwide integrative review of HEU, carried out in 2019, highlighted that the obstacles to the full operationalization of HEU included: lack of staff training; lack of institutional support; low prioritization by public management; failure to comply with the requirements

Chart 2. Distribution of included studies according to title, authors, journal and year of publication, study period, study location, study focus, objective and considerations.

Study title	Authors	Journal (year of publication)	Study period	Study location	Study focus	Objective	Considerations
Núcleos de epidemiologia em hospitais de alta complexidade da rede pública de saúde situados no Recife, Pernambuco: avaliação da implantação	Mendes, Freese, Guimarães[14]	Revista Brasileira de Saúde Materno Infantil (2004)	2000	Recife	S/P	Assess the degree of implementation of epidemiology units in seven highly complex hospitals in the public health network located in Recife.	During the implementation process of HEU, there are moments of progress and setbacks, influenced by contextual factors. In most of them, there are deficiencies in the physical and material structure, compromising their operation. One of the main obstacles to the implementation and operation of HEU is related to the lack of human resources as well as the need for training.
Avaliação da implantação dos núcleos hospitalares de epidemio-logia	Oliveira et al.[15]	Revista de Enfermagem UFPE online (2019)	2016	Piauí	S/P	Assess HEU implementation.	In general, all of them have made progress in carrying out active searches, data processing and investigation of notifiable diseases (ND). However, despite the positive results in terms of increasing the number of notifications, some institutions still have gaps in carrying out passive searches, and the data, even though consolidated, are not disclosed in a way that allows for timely intervention.
Três décadas de epidemiologia hospitalar e o desafio de integrar a Vigilância em Saúde: reflexões a partir de um estudo de caso	Escosteguy, Pereira, Medronho[16]	Ciência & Saúde Coletiva (2017)	2017	Rio de Janeiro	S/ P/ O	Report the experience of implementing and deploying the epidemiology service/HFSE.	The epidemiological surveillance routine is fully structured. The service is part of the Hospital Epidemiological Surveillance Network (REVEH - Rede de Vigilância Epidemiológica Hospitalar) of national interest, and plays an important role as a reporting unit within the municipality and the state.
Avaliação do Subsistema Nacional de Vigilância Epidemiológica em Âmbito Hospitalar no estado de Pernambuco, Brasil	Siqueira Filha, Vanderlei, Mendes[17]	Epidemiologia e Serviços de Saúde (2011)	2008	Pernambuco	S/P	Assess the degree of implementation of HEU that make up the Reference Hospital Network in Pernambuco.	The study highlights the need to implement policies for hiring and retaining qualified professionals, publicizing HEU activities in hospitals and in the epidemiological surveillance subsystem itself, expanding and increasing efficiency in the use of financial resources, and creating mobilization strategies to promote greater integration and exchange of successful experiences among HEU.
Vigilância epidemiológica e avaliação da atenção hospitalar à meningite	Escosteguy et al.[20]	Revista de Saúde Pública (2004)	1986 to 2022	Rio de Janeiro	P	Analyze the clinical-epidemiological profile and predictors of in-hospital death of patients with infectious meningitis admitted to a public hospital.	Epidemiological surveillance operating at the hospital level was able to provide feedback to services with care indicators, making the use of the Notifiable Diseases Information System (SINAN -Sistema de Informação de Agravos de Notificação) at this level pertinent.
Diagnóstico situacional da capacidade de resposta da rede hospitalar de emergência a eventos associados a viajantes internacio-nais em cidade-sede da Copa de 2014: estudo de caso de Brasília	Santos[22]	Dissertation (Master's in Public Health Epidemiology) (2013)	2013 to 2014	Brasília	S/ P/ O	Conduct a situational diagnosis of the response capacity of hospitals in the emergency network of Brasília to diseases, injuries and events requiring immediate mandatory notification of national and international interest.	After analysis, it was found that, of the 2,570 events reported to SINAN, less than 1% (0.4) were reported to CIEVS through the Public Health Event Monitoring System (SIME - Sistema de Monitoramento de Eventos em Saúde Pública).
Avaliação da Rede de Núcleos Hospitalares de Epidemiologia do Estado de São Paulo	Cardozo[23]	Dissertation (Master's in Public Health) (2018)	2017 a 2018	São Paulo	S/ P/ O	Describe and assess the HEU network in the state of São Paulo, from a structural point of view, with a focus on human resources and processes.	The HEU network assessment in the state of São Paulo was generally favorable regarding the process. Although the structural analysis was less favorable, as 15 HEU were classified as partially adequate, the majority had an adequate process. This study points to the need for adaptation of some HEU regarding the composition and workload of the team and suggests that discussions with the teams about the important role of producing analytical reports and using work process management tools.

Avaliação do Subsistema de Vigilância Epidemiológica em Âmbito Hospitalar – Rede de Núcleos Hospitalares de Epidemiologia do Estado de São Paulo	Luna et al[24]	Dissertation (Master's in Public Health) (2013)	2006 to 2011	São Paulo	S/P	Assess the epidemiological surveillance system in hospital settings – HEU network.	The implementation of the HEU network in hospitals improved the capture and investigation of cases of diseases subject to mandatory notification to the state surveillance system, however some activities in certain units can be improved.
Clima organizacional e satisfação laboral: um estudo sobre os Núcleos Hospitalares de Epidemiologia de Natal/RN	Matias[25]	Dissertation (Master's in Nursing) (2010)	2010	Natal	S/P	Identify the relationship between the organizational climate in the regulated HEU in the city of Natal and job satisfaction of the professionals who work there.	It is suggested that studies be carried out to verify how organizational culture, as an expressive internal factor, influences the establishment of the HEU's organizational climate and, consequently, the level of job satisfaction and individual well-being of its team members.
Conhecimento do enfermeiro sobre as ações de vigilância epidemiológica no hospital Universitário Onofre Lopes, Natal, RN	Ribeiro[9]	Dissertation (Master's in Nursing) (2010)	2010	Natal	P	Verify nurses' knowledge about the epidemiological surveillance actions at the Hospital Universitário Onofre Lopes (HUOL), in the city of Natal, state of Rio Grande do Norte.	Given the difficulties presented, it becomes important to recommend educational processes with a strategy for transforming practices, in addition to proposing actions in light of the principle of comprehensiveness, enabling agile and effective responses, in accordance with the purpose of HES, in the face of current epidemiological emergencies.
O processo de trabalho de enfermeiros em Núcleos Hospitalares de Epidemiologia	Medeiros et al.[26]	Cogitare Enfermagem (2014)	2012	Curitiba	S/P	Characterize HEU nurses' work process in terms of agents, purpose, means and instruments, object and products.	It was concluded that professional practice, in these units, must break with the task-centered model of action towards a model articulated with reference services and that contributes to the construction of public policies aligned with the health needs of the population.
Contribuição do Núcleo de Vigilância Epidemiológica em uma Unidade de Pronto Atendimento para a Notificação Compulsória de Agravos	Dantas et al.[7]	Revista Brasileira de Ciências da Saúde (2014)	2012 to 2014	João Pessoa	O	Demonstrate the contribution of the Epidemiological Surveillance Unit (ESU) actions of a 24-hour Emergency Care Unit (ECU) in the city of João Pessoa, PB.	The implementation of an ESU in an ECU presents a concrete contribution to the epidemiological surveillance system due to the possibility of increasing sensitivity and timeliness in detecting diseases that require compulsory notification.
Notificações de doenças compulsórias e dos agravos em um hospital Universitário de Minas Gerais, Brasil	Silva et al.[27]	Revista de Enfermagem da UFSM (2014)	2011 to 2012	Montes Claros	O	Analyze the notifications of compulsory diseases and the injuries recorded in a university hospital in northern Minas Gerais.	The study provided information on the epidemiological situation in the areas where they occur.
Núcleos Hospitalares de Vigilância Epidemiológica no Brasil: uma revisão integrativa de literatura científica	Lima et al.[28]	Revista de Epidemiologia e Controle de Infecção (2019)	2007 to 2017	Senhor do Bonfim	S/P	Assess, based on a literature review, the functioning of ESU in Brazil.	HEU stand out as a reference sector for carrying out compulsory notification and for managing situations involving notifiable diseases and diseases within hospital settings. Non-compliance with the requirements and competencies established in Ordinance 2,529/2004 was verified.
Vigilância em Saúde na atenção terciária: um estudo sobre os Núcleos Hospitalares de Epidemiologia	Picolli[29]	Dissertation (Master's in Nursing) (2015)	2015	Florianópolis	S/P/O	Highlight the surveillance actions developed by HEU in the Greater Florianópolis region, SC, and their articulation with other levels of healthcare.	HEU stands out as a reference sector for carrying out compulsory notification and for managing situations of communicable diseases, unusual diseases and emerging and re-emerging diseases, overcoming the barriers of hospital settings and playing an important role in communication between the points of the Healthcare Network.
Subnotificação das doenças de notificação compulsória no contexto hospitalar	Griep[30]	Dissertation (Master's in Nursing) (2003)	2001	Cascavel	S/P		The implementation of a continuing training program at local and municipal level complements the need for training and updating as well as providing an opportunity to discuss cases and data from reality, with the aim of adopting joint measures to address the epidemiological situations presented.

Vigilâncias hospitalar: possibilidades e obstáculos de uma prática integrada	Schettert[31]	Thesis (Doctoral in Public Health)) (2008)	2007	São Paulo and Rio de Janeiro	S/P/O	Identify, through historical analysis, the main elements that underpinned epidemiology as a science, addressing aspects of this as a basis for the development of epidemiological surveillance actions for communicable diseases in the country.	They recognize that a HES service requires standards, flows, protocols, etc. to integrate its practices, which requires building integration. Although they believe that integration should not begin with changing the structure of the service, but with the work process, they hope that, at the end of this construction, a regulation will be created that proposes the integration of surveillance, making the proposal effective.
Avaliação da Estratégia Nacional de Vigilância Epidemiológica Hospitalar	Ruy[35]	Dissertation (Master's in Public Health) (2017)	2008 to 2016	São Paulo and Rio de Janeiro	O	Discuss the issue of integrating surveillance in hospitals (HES and hospital infection control surveillance), analyzing the possibilities and impossibilities of this integration. Assess the network of HES units according to surveillance and financing models in Brazil between 2008-2016.	The change in the surveillance model has influenced the data produced by the Hospital Epidemiological Surveillance Network, but the strategy has proven effective over the years. Thus, the HES strategy supports the planning of health prevention and promotion actions, disease control, health problems and public health events, and guides decision-making at the three levels of Brazilian Health System management.

Caption: N: no; S: structure, P: process, O: outcome.
Source: developed by the author.

and competencies established in the regulation (Ordinance 2,529/2004); lack of periodic training; lack of preparation and publication of information generated by the units; insufficient research; lack of consistent monitoring of vital events in all units; lack of collaboration between unit technicians and Hospital Infection Control Committees (HICC); and underreporting of cases in some HEU.[21]

A study conducted in Brazil in 2015 sought to present the actions of HEU with other levels of healthcare, playing an important role in communication between the points of the Healthcare Network. The information obtained in hospital settings is of great importance and aids decision-making, contributing to meeting the health system's needs.[22]

A study carried out in a municipality of Cascavel in the state of Paraná revealed that underreporting notifiable diseases in hospital settings is a significant concern for health authorities and that there is a tendency to underestimate the real incidence of diseases due to several factors, such as lack of awareness, inadequate knowledge of notification protocols, reputational concerns and possible legal consequences.[23]

Seeking to verify an integrated practice between HES and Hospital Infection Control Service, a study carried out in the RJ-SP axis highlighted that collaboration between different types of surveillance, such as epidemiological and infection control, can result in a more comprehensive understanding of health risks. However, the research also identifies obstacles, such as the lack of effective communication between different teams and the lack of sharing of relevant data. [24]

In relation to searches for studies on HEU, we came across studies that present as the object of study, for instance, the diseases and injuries reported by the unit, such as healthcare-associated infections. However, these studies report, in parallel, on the organization functioning or system. From this, we can verify parts of the HES operationalization systematics, whether focusing on the structure, process or outcome. This occurs mainly in international studies.[25-28]

CONCLUSION

The study presented 18 publications of studies on structure and/or processes and/or outcomes on HEU, distributed nationwide.

It was identified that the studies address topics such as notification and investigation of diseases and injuries and active search. Some even verticalize analyses on integration between sectors within hospital settings and the external care network. However, there are few studies that analyze the performance of the units – analysis of process and outcomes, considering dissemination of information, promotion of control actions and assessment of the efficacy and effectiveness of the measures adopted. We emphasize that the performance of a HEU must contemplate all these activities.

For now, this study provides an overview of HEU in the scientific literature, allowing a broader view of HEU scenarios, although studies on this subject are scarce. We therefore highlight the importance of studies that investigate the functioning and work process of these operational units (HEU) within hospitals, as well as their contribution to public health.

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AUTHORS' CONTRIBUTIONS

Rodrigo Faria Dornelas contributed to literature review, abstract writing, introduction, methodology, discussion, interpretation and description of results, preparation of tables, and conclusions. **Ana Luiza Lima Sousa** contributed to article review (abstract, introduction, method, extraction table presentation, results, discussion, and conclusion) and suggestions. She conducted a comprehensive critical analysis of the content, identifying areas that required greater clarity, coherence, or depth.

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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REVIEW ARTICLE

Identification, resistance, and susceptibility of microorganisms on healthcare workers' hands: a systematic review and meta-analysis

Identificação, resistência e suscetibilidade de microrganismos nas mãos de profissionais de saúde: revisão sistemática e meta-análise

Identificación, resistencia y susceptibilidad de microorganismos en las manos de trabajadores de la salud: una revisión sistemática y meta-análisis

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Corresponding Author:
Juan Jairo Vaca-González
jjvacag@unal.edu.co

Address: Universidad Nacional de Colombia, Sede La Paz. Kilómetro 9, Vía Valledupar – La Paz, 202017.

Nolbedir Saza Ramírez[1];
Fernando Rojas Páez[1];
Julieth Yadira Serrano Riaño[2];
Juan Jairo Vaca-González[3];

[1] *Facultad de Ciencias de la Salud, Universidad del Quindío, Armenia, Colombia.*
[2] *Escuela de Pregrado, Dirección Académica, Vicerrectoría de Sede, Universidad Nacional de Colombia, Sede de La Paz, Cesar, Colombia.*
[3] *Universidad Nacional de Colombia, Sede La Paz, Bolívia.*

ABSTRACT

Background and Objectives: The aim of this study is to analyze, through a systematic review and meta-analysis, the identification, resistance and susceptibility of microorganisms present in healthcare workers' hands, identifying the most relevant antimicrobial resistant bacteria and their prevalence. **Methods:** Several scientific databases were reviewed to summarize contributions of the past 10 years. A meta-analysis was conducted to assess bacteria on healthcare workers' hands and their resistance and susceptibility profiles. **Results:** healthcare workers were colonized by 35 types of bacteria, highlighting *Staphylococcus aureus*., *Acinetobacter spp.*, and *Escherichia. coli*. Although a lower number of bacteria was present on healthcare workers' hands, doctors acquired more bacteria. Specifically, health personnel contracted *Enterococcus spp.*, *Staphylococcus. epidermis*, *Acinetobacter spp.*, *Escherichia. coli*, among others. Resistance and susceptibility profiles showed that *S. aureus* was susceptible to antibiotics; nevertheless, *S. aureus* was resistant to ceftriaxone, erythromycin and amoxicillin-clavulanic acid. **Conclusion:** Detected microorganisms trigger pathologies of clinical importance such as skin infections, sepsis, gastroenteritis, among others; in addition, bacteria are the cause of pathologies of greater clinical importance, such as nosocomial pathologies due to work activity in the hospital environment, which require invasive treatment. Even if new drugs are developed, the way of prescribing and using antibiotics needs to be changed to reduce antibiotic resistance.

Keywords: *Cross Infection. Community-Acquired Infections. Bacterial Drug Resistance. Hand Disinfection. Health Personnel.*

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RESUMO

Justificativa e Objetivos: O objetivo deste estudo é analisar, por meio de uma revisão sistemática e metanálise, a identificação, resistência e suscetibilidade de microrganismos presentes nas mãos de profissionais de saúde, identificando as bactérias mais relevantes e sua prevalência à resistência aos antibióticos. **Métodos:** Diversas bases de dados científicas foram revisadas para resumir as contribuições dos últimos 10 anos. Foi realizada uma meta-análise para avaliar bactérias nas mãos dos profissionais de saúde e os seus perfis de resistência e suscetibilidade. **Resultados:** os profissionais de saúde foram colonizados por 35 tipos de bactérias, destacando-se *Staphylococcus aureus., Acinetobacter spp.* e *Escherichia. coli*. Embora o número de bactérias nas mãos dos profissionais de saúde fosse menor, os médicos adquiriram mais bactérias. Especificamente, o pessoal de saúde contraiu *Enterococcus spp., Staphylococcus. epiderme, Acinetobacter spp., Escherichia. coli,* entre outras. Os perfis de resistência e suscetibilidade mostraram que *S. aureus* era suscetível a antibióticos; no entanto, *S. aureus* foi resistente à Ceftriaxona, Eritromicina e Amoxicilina-Ácido Clavulânico. **Conclusão:** Os microrganismos detectados desencadeiam patologias de importância clínica como infecções de pele, sepse, gastroenterites, entre outras; além disso, as bactérias são causadoras de patologias de maior importância clínica, como as patologias nosocomiais decorrentes da atividade laboral no ambiente hospitalar, que requerem tratamento invasivo. A forma de prescrever e usar antibióticos precisa ser alterada, mesmo que novos medicamentos sejam desenvolvidos, para reduzir a resistência aos antibióticos.

Descritores: *Infecção Hospitalar. Infecções Comunitárias Adquiridas. Farmacorresistencia Bacteriana. Desinfecção das Mãos. Pessoal de Saúde.*

RESUMEN

Justificación y Objetivos: El objetivo de este estudio es analizar, mediante una revisión sistemática y un metaanálisis, la identificación, resistencia y susceptibilidad de los microorganismos presentes en las manos de los trabajadores de la salud, identificando las bacterias más relevantes y su prevalencia de resistencia a los antibióticos. **Métodos:** Se revisaron varias bases de datos científicas para resumir las contribuciones de los últimos 10 años. Se realizó un metaanálisis para evaluar las bacterias en las manos de los trabajadores de la salud y sus perfiles de resistencia y susceptibilidad. **Resultados:** los trabajadores de la salud fueron colonizados por 35 tipos de bacterias, destacando *Staphylococcus aureus., Acinetobacter spp.* y *Escherichia. coli*. Aunque las bacterias en las manos de los trabajadores de la salud fueron menores, los médicos adquirieron más bacterias. En concreto, personal sanitario contrajo *Enterococcus spp., Staphylococcus. epidermis, Acinetobacter spp., Escherichia. coli,* entre otros. Los perfiles de resistencia y susceptibilidad mostraron que *S. aureus* era susceptible a los antibióticos; sin embargo, el *S. aureus* fue resistente a ceftriaxona, eritromicina y amoxicilina-ácido clavulánico. **Conclusión:** Los microorganismos detectados desencadenan patologías de importancia clínica como infecciones de la piel, sepsis, gastroenteritis, entre otras; además, las bacterias son causantes de patologías de mayor importancia clínica, como las patologías nosocomiales debidas a la actividad laboral en el ámbito hospitalario, que requieren un tratamiento invasivo. Es necesario cambiar la forma de prescribir y utilizar los antibióticos, incluso si se desarrollan nuevos medicamentos, para reducir la resistencia a los antibióticos.

Palabras Clave: *Infección Hospitalaria. Infecciones Comunitarias Adquiridas. Farmacorresistencia Bacteriana. Desinfección de las Manos. Personal de Salud.*

INTRODUCTION

According to the World Health Organization (WHO), inequalities between high- and lower-income countries regarding proper hand hygiene facilities need to be reduced, since only 1 in 10 healthcare workers have appropriate hand hygiene practices while caring for patients at high risk of healthcare-associated infections (HAIs).[1] Inadequate hygiene can lead to the spread of high-risk bacteria. Notably, healthcare workers' hands have tested positive for gram-negative bacteria such as *Enterococcus spp.* (19.7%), *Pseudomonas spp.* (13.7%), *Escherichia. coli.* (*E. coli)* (4.2%), *Klebsiella oxytoca* (1.4%), and *Enterococcus faecalis* (1.4%).[2] Similarly, a study focused on hands of nurses showed that they were colonized by *S. epidermidis* (64.7%), *Staphylococcus. warneri* (63%), *Enterococcus faecalis* (7.5%), *Staphylococcus hominis* (5.1%) and *Enterobacter agglomerans* (4.2%).[3] A recent study of doctors, residents and nurses was conducted to assess bacterial load on their hands. Results showed that hands were colonized by *S. aureus* (10.6%), *Coagulase Negative Staphylococcus* (7.4%), aerobic spore bearing bacilli (3.2%), *E. coli* (3.2%), *Pseudomonas spp.* (1.1%) and *Acinetobacter spp.* (1.1%).[4] These data indicates that healthcare workers' hands elevate the risk of transmitting pathogens to vulnerable patients, potentially leading to HAIs. Additionally, the presence of multidrug-resistant bacteria on hands can contribute to the dissemination of antibiotic-resistant strains, further compromising

treatment efficacy. In fact, there is evidence that HAIs result from nosocomial cross-infection propagated by microorganism transmission between patients, primarily via healthcare professionals' hands.[5] Elevated bacterial presence on personnel hands also relates to heightened bacterial resistance and multi-resistant strains,[6] linked to healthcare system collapse, self-medication, rampant hospital antibiotic use, false security, and improper protective equipment use.[7] Some studies have detected multidrug-resistant bacteria on healthcare workers' hands, including methicillin-resistant *Staphylococcus aureus* (11.2%), vancomycin-resistant *Enterococci* (10%), multidrug-resistant *Pseudomonas aeruginosa* (17.4%), and multidrug-resistant *Acinetobacter baumannii* (29.3%).[8] Salehi et al. highlighted *Acinetobacter baumannii's* extensive drug resistance (40%) and multidrug resistance (100%) against various antimicrobials (e.g., ceftriaxone, ciprofloxacin, meropenem, gentamicin, tigecycline).[9] Regarding bacteria isolated from healthcare workers' hands, significant resistance was observed: *S. aureus* to oxacillin (59.6%), *A. baumannii* to imipenem (54.4%), ciprofloxacin (63.3%), amoxiclav (100%), lomefloxacin (63.3%), cefotaxime (100%), piperacillin (54.5%), cefepime (54.4%), *Streptococci* to gentamicin (100%), sulfamethoxazole (62.5%), and *Enterococcus spp.* to sulfamethoxazole (100%).[10] Most multidrug-resistant bacteria stem from patients with infected wounds, with coagulase negative staphylococci and *S. aureus* displaying 100% resistance to penicillin and ampicillin. Both demonstrated 100% and 91.7% resistance to oxacillin, respectively.[11] Colombia's Ministry of Health analysis in ICUs noted *K. pneumoniae* and *E. coli* resistance to cephalosporins (37% and 26.9%, respectively), while *A. baumannii* and *P. aeruginosa* showed carbapenem resistance (31% and 37.8%, respectively). Gram-positive bacteria are oxacillin-resistant (37.8%), and *E. faecium* showed vancomycin resistance (22.3%).[12]

Building upon the previously mentioned, the identification, resistance, and susceptibility of microorganisms isolated from the hands of healthcare workers represent a critical area of concern. Bacterial resistance and susceptibility, though subject to advances in pharmacological research, pose significant threats to overall health. Governmental interventions and research endeavors play essential roles in mitigating the adverse effects of these microorganisms on healthcare workers' hand hygiene practices.[13] Studies have underscored the need for periodic bacterial population assessments among healthcare workers to discern pathogen prevalence and distribution based on professional roles.[14] Adherence to established clinical and surgical handwashing protocols remains a crucial aspect to ensure effective hygiene practices. Based on this, conducting a systematic review and meta-analysis on the identification, resistance, and susceptibility of microorganisms on healthcare workers' hands will address critical gaps, including global disparities in hand hygiene practices, comprehensive identification of bacterial colonization, and in-depth understanding of resistance patterns. It will assess variations in bacterial load and pathogen prevalence among different professional roles, develop evidence-based infection control strategies, identify common trends and variations in resistance, and highlight gaps to guide future research. Moreover, this study aims to enhance overall healthcare safety by reducing pathogen transmission, thereby protecting both healthcare professionals and patients from microbial resistance threats. By pooling data from diverse sources, it becomes possible to derive more accurate and generalized insights, identifying common trends, variations, and potential outliers. This approach offers a more nuanced understanding of the prevalence, mechanisms, and implications of bacterial resistance and susceptibility, contributing to evidence-based strategies for infection control. Furthermore, such an approach can highlight gaps in knowledge, guide future research directions, and inform decisions aimed at optimizing hand hygiene practices among healthcare workers. Ultimately, a systematic review with meta-analysis serves as a crucial tool for evidence-driven advancements in healthcare practices, safeguarding both medical professionals and patients against the threats posed by microbial resistance.[15] For this reason, the objective of this investigation is to analyze, through a systematic review and meta-analysis, the identification, resistance and susceptibility of microorganisms present in healthcare workers' hands, identifying the most relevant antimicrobial resistant bacteria and their prevalence. Although the field of research is broad on this topic, the constant change in hospital practices and microbial behavior requires an in-depth analysis based on what has been published by other authors. Research studies, especially those utilizing meta-analysis, enable informed decision-making in everyday hospital settings by revealing resistance and susceptibility patterns, the prevalence of microorganisms among healthcare workers, and thus help reduce the risk of HAIs in patients. Additionally, this information is valuable for healthcare professionals themselves, as it contributes to the proactive management and prevention of disease transmission. Overall, this study moves forward on developing targeted intervention strategies to improve hand hygiene practices across different healthcare settings, especially in low-income countries. Additionally, the results may be useful to perform longitudinal studies that monitor the effectiveness of these interventions over time and assess changes in bacterial colonization and resistance patterns. Research should also explore the molecular mechanisms of resistance to develop new antimicrobial agents and enhance existing treatments. Furthermore, investigations into the impact of education and training programs on healthcare workers' adherence to hand hygiene protocols could provide valuable insights. Finally, implementing real-time surveillance systems to track pathogen prevalence and resistance trends would be crucial for informing dynamic, evidence-based infection control policies.

METHODS

This research was executed within the framework

defined by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA - 2020) guidelines, serving as a methodological avenue to comprehensively, transparently, and accurately dissect data pertaining to the resistance and susceptibility profiles of microorganisms isolated by healthcare personnel.

This systematic review included studies focused on identifying microorganisms present on the hands of healthcare personnel, as well as those examining bacterial resistance and susceptibility profiles of such microorganisms. The inclusion criteria for this study w ere observational studies that investigated the colonization of healthcare workers' hands by microorganisms and their antibiotic resistance profiles. Eligible studies involved healthcare professionals, including doctors, nurses, and nursing assistants, who were exposed to microorganisms in clinical settings, and reported data on bacterial identification and susceptibility/resistance to antibiotics using standardized methods such as antibiograms. Additionally, the studies needed to clearly report the number of healthcare professionals with and without bacterial colonization, allowing for direct comparison between these two groups. Only studies published between 2010 and 2020 in English or Spanish were considered. Exclusion criteria encompassed intervention studies, clinical trials, and studies focusing solely on patient populations or non-clinical staff. Studies lacking detailed microbiological data, without standardized methods for resistance testing or with a high risk of bias were excluded, as were non-peer-reviewed sources like conference abstracts, book chapters, and gray literature.

A systematic inquiry was conducted to gather scientific evidence concerning the categorization, resilience, and vulnerability of microorganisms isolated from healthcare workers' hands. The investigation adhered to a structured PECO approach: P: Healthcare professionals, including doctors, nurses, nursing assistants, surgical instrumentalists, exposed to colonization by resistant microorganisms on their hands and practicing hand hygiene to mitigate HAIs. E: Exposure to microorganisms on the hands of healthcare personnel, measuring the prevalence of antibiotic-resistant bacteria. C: A comparison was made between the groups of healthcare personnel with the presence of the most frequent bacteria; moreover, an assessment of the resistance of these bacteria to different antibiotics commonly used in the hospital setting was performed. O: Identification of the most common bacterial groups in healthcare personnel, as well as the determination of those bacteria with the greatest resistance to different antibiotics, characterizing the resistance profiles to key antibiotics among the predominant bacteria. Simultaneously, a comprehensive search strategy was implemented to identify relevant research articles across various medical databases and governmental health entities. The databases searched included PubMed/MEDLINE, Web of Science, CINAHL, Embase, Cochrane CENTRAL, and SciELO. The search strategy was developed using a combination of controlled vocabulary terms derived from the Spanish (Descriptores en Ciencias de la Salud, DeCS) and English (Medical Subject Headings, MeSH) thesaurus, as well as free-text keywords. Both English and Spanish language articles were considered. Key search terms included 'bacteria,' 'microbial resistance,' 'healthcare workers,' and 'hand hygiene,' among others. Boolean operators, specifically 'AND', were used to combine search terms effectively. Additionally, the search strategy was refined iteratively by including terms such as 'antibiotic sensitivity,' 'health personnel,' 'drug-resistant bacteria,' 'hand,' 'antibiogram,' and 'susceptibility.' Filters and limits were not applied during the initial search to ensure inclusivity of relevant literature.

Two independent investigators conducted the screening process using the designated keywords and methodologies outlined in the study protocol. All titles and abstracts retrieved from the search engines were reviewed for potential inclusion in the analysis. Any discrepancies between the two reviewers were resolved through discussion or consultation with a third reviewer if necessary. Full-text articles of potentially relevant studies were obtained and assessed against the predetermined inclusion criteria. Data extraction was performed using a standardized data collection form, which included fields for recording information such as resistant and multi--resistant bacterial strains, quantification methodologies, clinical relevance, and significance to hand hygiene practices. The organized tabulation facilitated systematic assimilation and identification of pertinent data regarding bacterial agents associated with hand hygiene.

To assess the risk of bias within included studies, each investigator independently evaluated various elements including random sequence generation, blinding procedures, handling of incomplete data and outcomes, and other potential sources of bias, using established tools such as the Cochrane Risk of Bias Tool or the Newcastle-Ottawa Scale for observational studies. Any discrepancies in the assessment of bias were resolved through discussion or consultation with a third reviewer. Furthermore, the quality appraisal of included studies, data synthesis methods, assessment of study duplication, blinding procedures, and potential sources of bias were collaboratively reviewed by the two investigators to ensure consistency and accuracy in the interpretation of findings. Automation tools were not utilized in the screening or data extraction process.

The data preparation for presentation and synthesis involved employing the Mantel-Haenszel statistical approach to analyze dichotomous data, utilizing risk ratios (RR) accompanied by a 95% confidence interval (CI). The RR was calculated to compare the likelihood of bacterial colonization between the two defined groups. The first group consisted of healthcare professionals with bacterial presence on their hands, while the second group included those without bacterial colonization. Although the total population size was the same for both groups, the RR was used to quantify the difference in colonization risk between them. The RR calculations were based on 2x2 contingency tables, comparing the events (bacterial colonization) and non-events. A meti-

culous review of the literature was conducted to address missing summary statistics, and efforts were made to contact study authors for any necessary data clarification or supplementation. Tabulation and visual display of results were achieved through the use of forest plots, allowing for a clear representation of individual study findings and facilitating comparison across studies. The synthesis of results was based on a rationale grounded in the nature of data and the research question. Statistical heterogeneity was assessed using the I^2 statistic, with a threshold of $I^2 > 50\%$ indicating substantial heterogeneity. A fixed-effects model was employed in the absence of significant heterogeneity ($I^2 < 50\%$, $P > 0.1$), while a random-effects model was utilized when heterogeneity was observed. Sensitivity analyses were conducted to assess the robustness of synthesized results, ensuring the reliability of findings. The statistical software Revman 5.4.1 (Cochrane, London, United Kingdom) was utilized for analysis, with a significance level set at $p < 0.05$. These rigorous methods allowed for comprehensive exploration and synthesis of the available evidence, while maintaining transparency and reproducibility in accordance with PRISMA guidelines.[16]

RESULTS AND DISCUSSION

Data selection

Thirteen research articles were discerned for executing the respective systematic review and meta-analysis. Adhering to the PRISMA-2020 guidelines, the selection process is illustrated in Figure 1. Initially, 80 articles pertinent to hand hygiene in healthcare professionals were identified, of which 67 were excluded due to non-conformance with inclusion criteria. Subsequently, 14 research articles were deemed suitable for inclusion in the meta-analysis.

Bacteria identification on hands of healthcare personnel

The frequency of the most prevalent bacteria identified in the research studies concentrating on hand hygiene practices among healthcare personnel is delineated in supplementary material 1. Conforming to the frequency analysis, a Total staff/Total bacteria ratio was discerned, highlighting a cumulative total of 3,187 healthcare workers participating in hand hygiene activities, within which 2,257 bacterial specimens were ascertained. Particularly noteworthy among the bacteria frequently encountered on healthcare personnel's hands were *S. aureus* (377), *Acinetobacter spp.* (339), *Staphylococcus spp.* (316), *S. epidermidis* (294), *CoNS* (284), *Enterobacter* (109), and *E. coli* (75), among others. Conversely, less frequently observed bacteria included *Citrobacter spp* (7), *K species* (5), *Klebsiella spp.* (5), *Enterobacter aerogenes* (4), *Serratia* (4), and *Streptococcus pneumoniae* (2).

Resistance profiles and susceptibility to antibiotics in the bacteria present in the hands of healthcare personnel

The presence and absence of bacteria on the hands of healthcare personnel are delineated in Figure 2A. The outcomes revealed that 571 healthcare workers manifes-

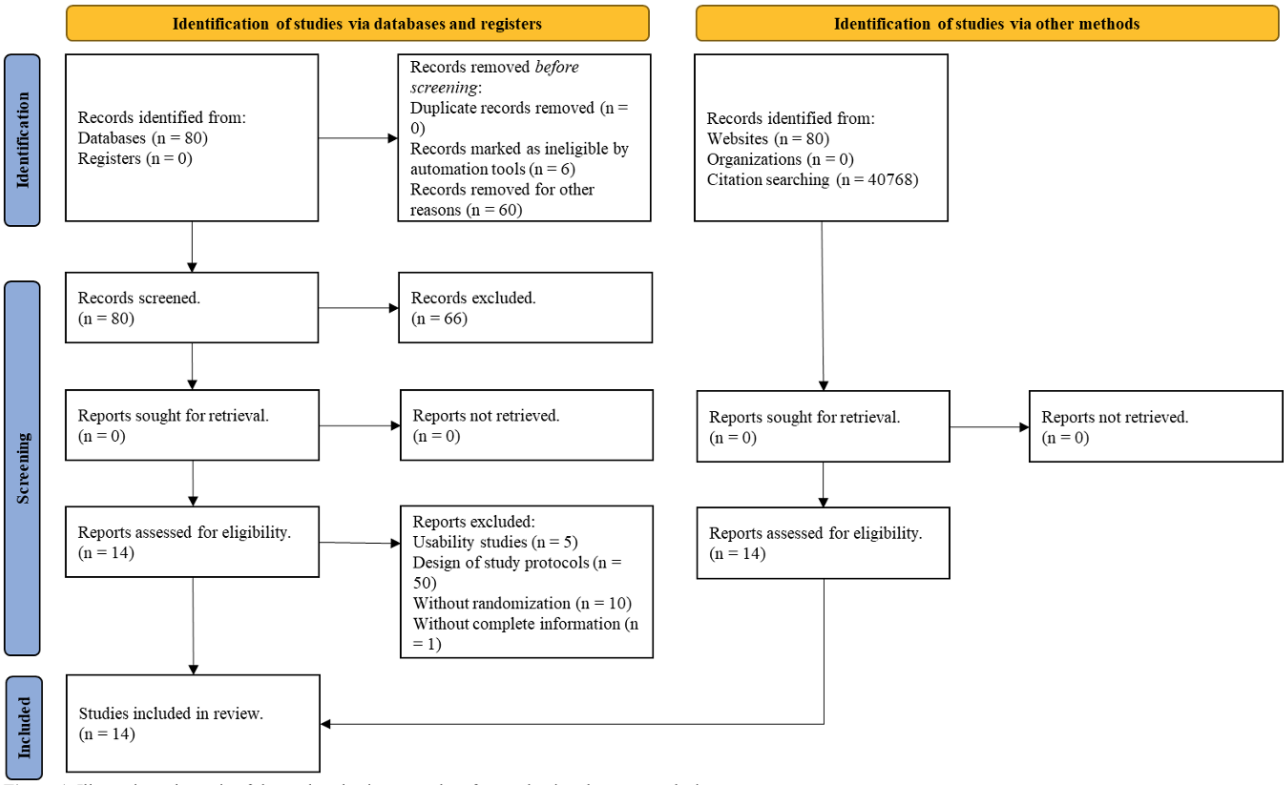

Figure 1. Illustrative schematic of the study selection procedure for conducting the meta-analysis.

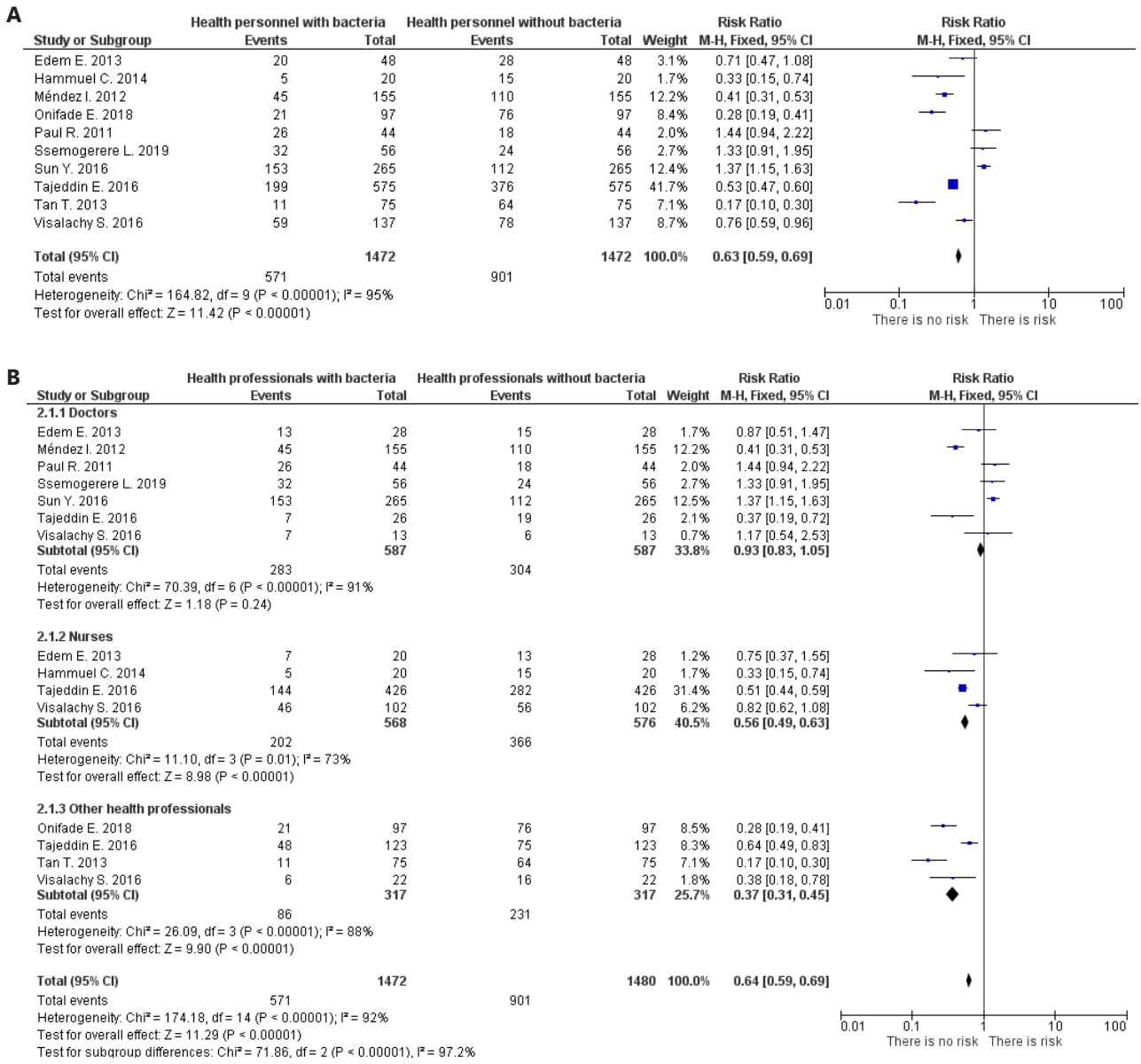

Figure 2. A) Presence and absence of bacteria in healthcare workers (studies conducted between 2011-2019). **B)** Bacterial occurrence among doctors, nurses, and other healthcare personnel (studies conducted between 2011-2019).

ted bacterial colonization on their hands, while 901 health personnel demonstrated an absence of pathogenic bacteria. However, the research conducted by Sun et al.[17] indicated that their study cohort stood as the singular group in which the presence of bacteria on healthcare personnel's hands exhibited statistical significance ($p < 0.00001$). Considering the aforementioned information, a more comprehensive analysis was undertaken to ascertain the specific healthcare personnel vulnerable to bacterial exposure. In this context, Figure 2B illustrates that in general, doctors, nurses, and other healthcare staff do not exhibit predisposition to bacterial colonization on their hands ($p < 0.00001$); however, the study by Sun et al.[17] revealed that the subgroup of doctors has the most substantial risk of bacterial acquisition ($p < 0.00001$).[17]

An analysis was executed to discern the bacterial taxonomy evident on the hands of healthcare workers (Figure 3). In accordance with the conducted analysis, healthcare personnel did not exhibit exposure to pathogens such as *Enterococcus spp.*, *Acinetobacter spp.*, *E. coli*, *Pseudomonas spp.*, and *Bacillus spp.*[8] Nonetheless, studies undertaken by Sun et al.[17] and Tajeddin et al.[10] demonstrated that the hands of healthcare personnel harbored *S. aureus* and *S. epidermidis*, respectively ($p < 0.00001$).

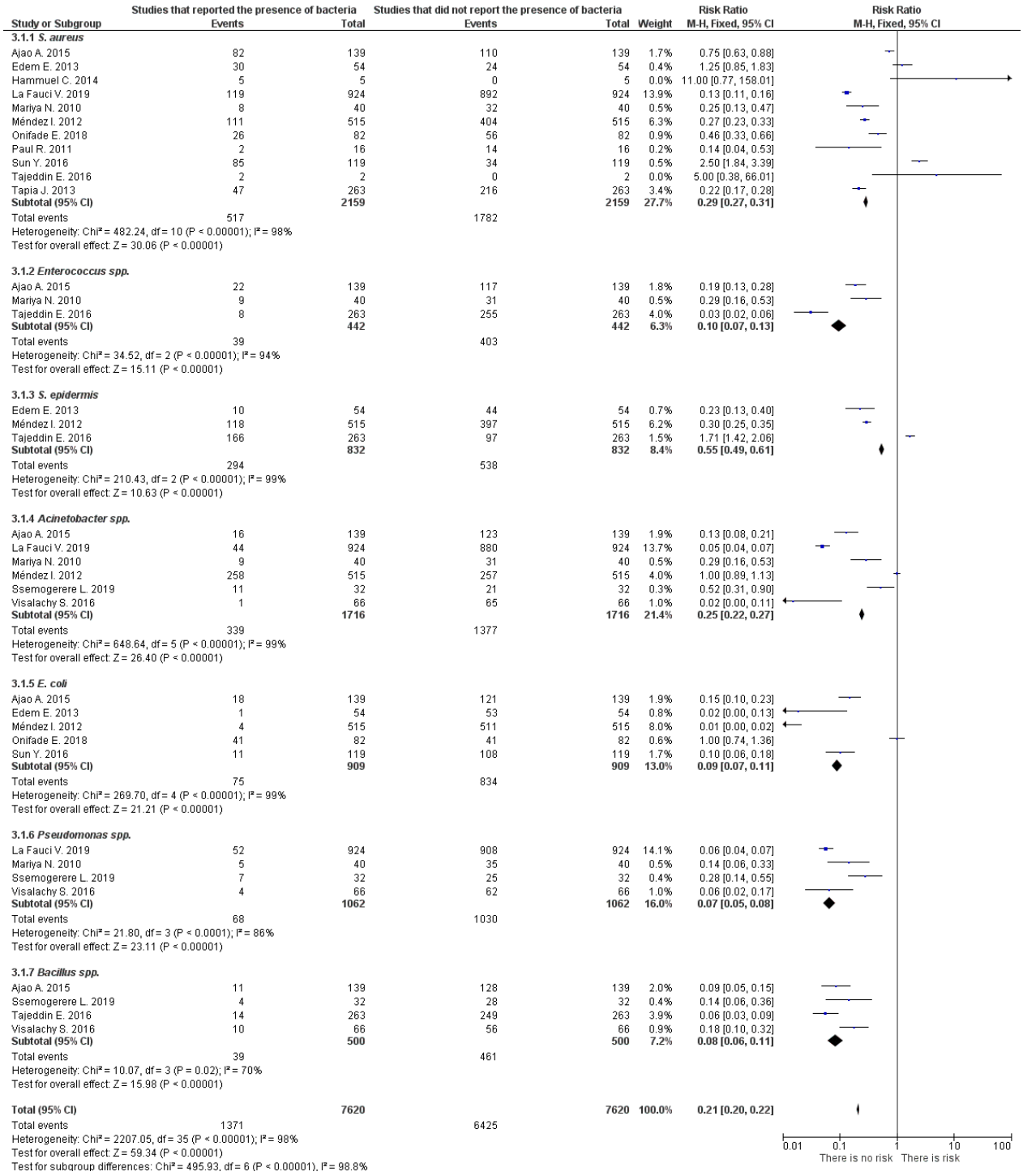

Figure 3. Taxonomic categorization of distinct bacterial species detected and absent on the hands of healthcare workers (studies conducted between 2011-2019).

According to the findings of our analysis, *S. aureus* emerges as the predominant bacteria on healthcare personnel's hands. Significantly, the statistical analysis underscored the susceptibility of *S. aureus* to antibiotics including ampicillin, vancomycin, and ofloxacin ($p < 0.00001$). Consequently, a statistical examination was conducted to delineate the resistance and susceptibility pattern of this pathogen towards various antibiotics (Figure 4). The results revealed that antibiotics such as erythromycin,[17,18] oxacillin,[10] ceftriaxone,[18,19] gentamicin and augmentin,[18] erythromycin and ciprofloxacin,[20] exhibited a substantial degree of resistance in combating the effects induced by *S. aureus* ($p < 0.00001$).

Acinetobacter is another bacterial genus displaying antimicrobial resistance among healthcare workers' hands. For instance, the study conducted by Ajao et al. ascertained that *Acinetobacter* demonstrated resistance against gentamicin ($p < 0.00001$) (Figure 5A).[21] No statistical significance was observed in the remaining investigations. Another highly relevant microorganism that was

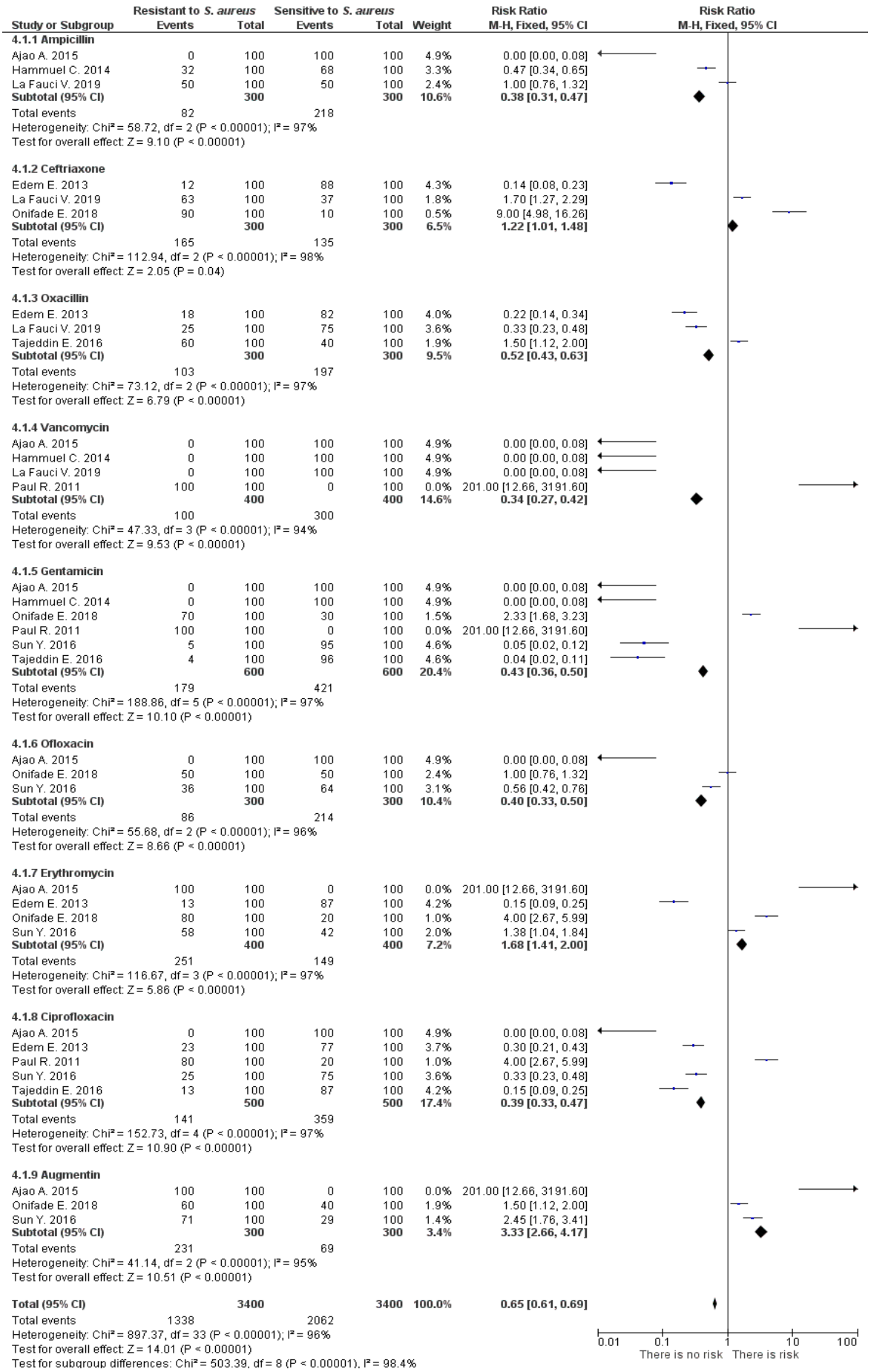

Figure 4. Bacterial resistance and susceptibility of S. aureus to different antibiotics (studies conducted between 2011-2019).

identified in this meta-analysis was *E. coli* (Figure 5B). The analysis evidenced that *E. coli* tends to be sensitive to antibiotics such as gentamicin, ofloxacin and ciprofloxacin ($p < 0.00001$). However, in the study carried out by Ajao et al. it was found that *E. coli* was resistant to Amoxicillin ($p < 0.00001$).[21]

This study associates bacterial presence/absence with healthcare workers' hands, thus evidencing that out of a total of 587 doctors, only 283 were in contact with bacteria. The study conducted by Sun et al.[17] was the most representative, revealing 156 bacteria; followed by the studies carried out by,[20,22-24] all of which identified bacterial colonization on the hands of the medical personnel.[24-28] Similarly, in comparison to,[29] this study demonstrates the presence of pathogens like *S. aureus* and *Pseudomonas aeruginosa* on healthcare personnel's hands. Conversely, bacteria correlate with presence/absence, highlighting 23% *S. aureus* incidents in all samples (517/2,159). This emphasizes significant risk of bacterial acquisition according to several authors.[10,17,23-26,30] Likewise, 39 instances *of Enterococcus spp* were identified out of a total of 442 reviewed bacteria. However, data found during the analysis were insufficient to statistically identify the presence of bacteria on healthcare workers' hands. In a similar vein, there were 294 occurrences of *S. epidermidis* out of 832 reviewed bacteria. Consequently, it was observed that, as per Tajeddin et al.[10] *S. epidermidis* holds a relatively noteworthy potential for contraction.[23] Correspondingly, the *Acinetobacter spp.* were identified in 339 instances out of 1,716, indicating that these bacteria do not hold significant prominence in the risk of contraction.[31] As for *E. coli* bacteria, they were identified in 75 occurrences out of a total of 909 reviewed bacteria. This shows that these bacteria carry a relatively noteworthy potential for contraction, as indicated by the study conducted by Onifade et al.[18] Concerning *Pseudomonas*, 68 instances were identified; however, upon analysis, it was observed that there is no significant data supporting the acquisition of the pathogen. Lastly, 39 occurrences were discovered for *Bacillus spp*, presenting statistically significant data that indicate the potential for contracting this type of bacteria.

Concerning bacterial presence among healthcare workers, this investigation unveiled 571 instances out of 1,472. Notably, doctors, nurses, and other healthcare professionals display limited awareness of hand bacterial colonization,[22,24] whereas doctors and nurses, according to,[17,20,23] exhibit relatively significant susceptibility to diverse bacterial strains. As supported by Avadhani et al. proper hand hygiene is vital in curbing infection transmission by medical and nursing personnel.[32] Similarly, *E. coli* pathogens are detected in healthcare personnel's hands due to fecal contamination, signaling deficient post-toilet hand hygiene. The analyzed studies identify a minimum presence of two pathogens among 20 healthcare workers, contrasting with up to 924 bacteria in 1,848 health professionals.[24,26,27,30]

Based on the sensitivity profile and bacterial resistance, it has been identified that, according to the list of antibiotic-resistant microorganisms released by the PAHO in 2021, *S. aureus* currently exhibits sensitivity to broad-spectrum antibiotics.[33] Among these, the clinical significance of vancomycin's action spectrum is noteworthy, as it displays reduced efficacy in counteracting bacterial effects during potential infections. In the study conducted by Paul et al.[20] a reduced risk of *S. aureus* acquisition was observed; however, the efficacy of protective measures through drug intervention is diminishing due to the emergence of resistant strains.[28] Similarly, as indicated by Rodríguez et al.[34] vancomycin resistance is indeed present in *S. aureus*, attributed to cell wall modifications that sequester the antibiotic before it reaches the site of action, thereby failing to achieve the desired bactericidal effect. According to the findings of this study, it was evident that 82 cases out of a total of 300 occurrences of *S. aureus* were resistant to ampicillin, while 218 cases exhibited sensitivity. Consequently, a significant risk in harboring the pathogen is evident.[19] Accordingly to the PAHO, *S. aureus* resistance, particularly in cases involving methicillin and vancomycin, constitutes the highest critical risk, yet devoid of clinical significance.[33] Bacterial resistance and susceptibility of *Acinetobacter* to gentamicin were observed in 121 cases, while 179 occurrences demonstrated sensitivity. In the study conducted by La Fauci et al.[19] insignificance in the risk of bacterial containment was noted. According to the PAHO, gentamicin has shown resistance against *Acinetobacter*, as it is categorized as an aminoglycoside rather than a carbapenem.[33] In studies carried out by,[18,19] *E. coli* exhibited a heterogeneity of 97% in comparison to gentamicin and ofloxacin, signifying insignificance in risk. Conversely, against ciprofloxacin and amoxicillin, it presented a very low point estimate with weak evidence, suggesting no statistical difference from effects shown in studies by various authors. This demonstrates sensitivity of this pathogen to ciprofloxacin (77.1%) and amoxicillin (93.1%), highlighting effective management against its impact on at-risk populations' health.[35]

Various antibiotics—such as gentamicin, ofloxacin, oxacillin, vancomycin, ciprofloxacin, Augmentin, ampicillin, and ceftriaxone—are employed to counter pathogens including *S. aureus, Enterococcus spp., S. epidermidis, Acinetobacter spp., E. coli, Pseudomonas spp.*, and *Bacillus spp.* Nonetheless, varying degrees of bacterial resistance emerge. Verification requires cultures and antibiograms for optimal management considering cost, availability, administration, and response times to bacterial colonization. Studies evaluating healthcare workers' hand hygiene practices, conducted by,[33,35] reveal that 45% perceived good knowledge, while 55% perceived moderate knowledge. These findings underscore the responsibility of health professionals to ensure habitual hand hygiene adherence, prioritizing it institutionally. Limitations surfaced during analysis, with some studies failing to distinguish between bacterial resistance and susceptibility percentages. Certain studies even omitted pathogen identification despite stated focus. Similarly, biological constraints emerged, accompanied by lack of precision

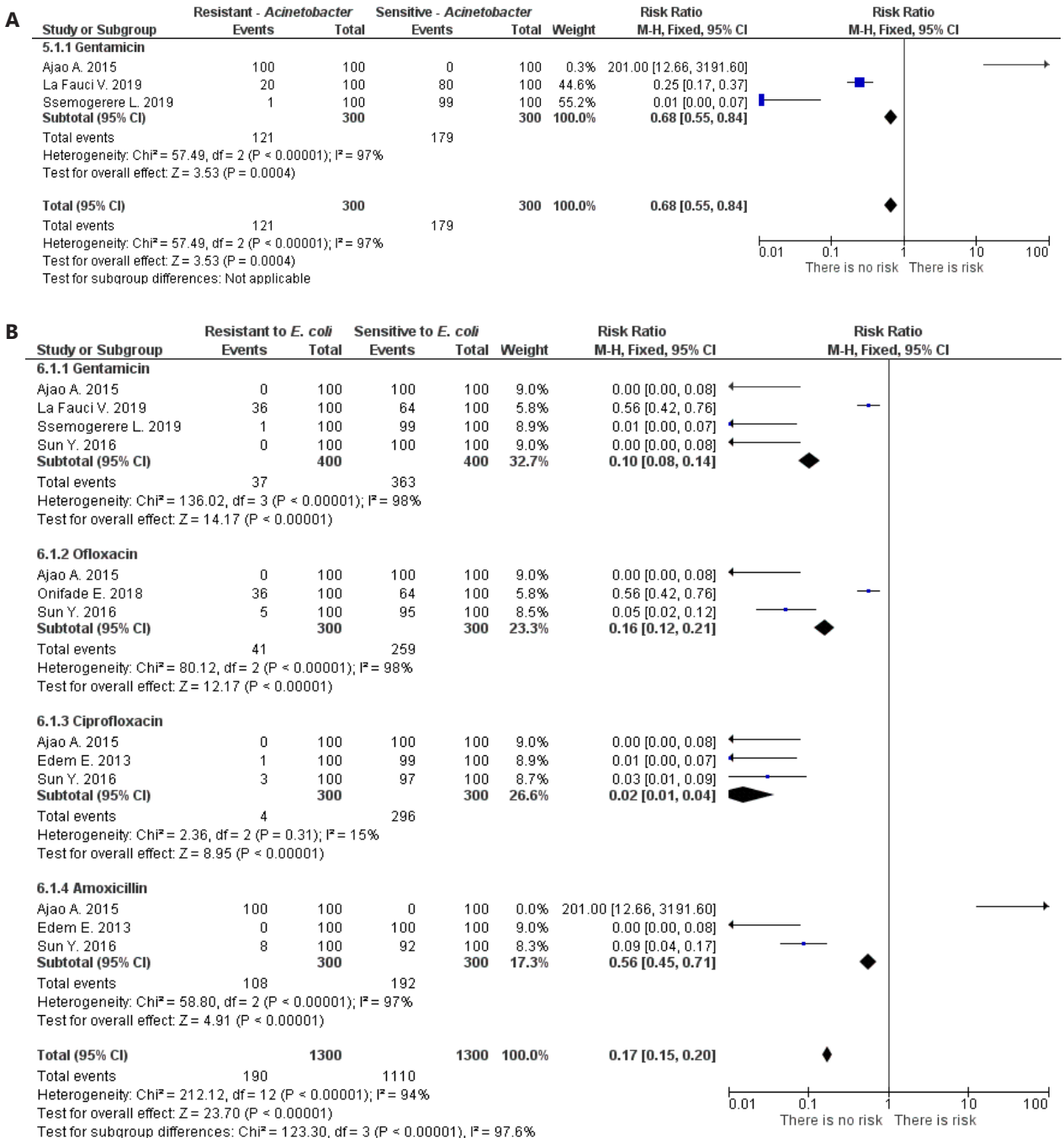

Figure 5. A) Bacterial resistance and susceptibility of Acinetobacter to gentamicin (studies conducted between 2015-2019). **B)** Resistance and sensitivity of antibiotics to E. coli to different antibiotics (studies conducted between 2013-2019).

in defining the healthcare professional population and study sample for hand hygiene assessment.

In general terms, hand hygiene has gained prevalence over the last two years as a prominent defense against COVID-19.[36] Yet, its significance extends beyond recent times, encompassing years of use in combating HAIs and the dissemination of multidrug-resistant microorganisms.[37] Despite handwashing being championed as an efficient, cost-effective approach to curbing HAIs, compliance remains notably low among healthcare workers in both developed and developing nations.[38] An investigation examining hand hygiene awareness among 289 healthcare workers observed noteworthy outcomes. After interventions, handwashing adherence considerably improved in pediatrics, internal medicine, and obstetrics-gynecology departments. Health personnel perception concerning the likelihood of hospitalized patients developing HAIs also significantly rose from 49.7% to 58.6% post-intervention.[39] In a comparable study, findings revealed gaps in handwashing infrastructure, where units lacked hand hygiene posters or policies, alcohol-based hand rubs, and few toilets had flowing tap

water throughout the day. In terms of healthcare workers behavior, some of them performed handwashing before patient contact, before aseptic procedures, after potential body fluid exposure, and following patient interactions.[39] Genc et al. investigated to gauge nasal *S. aureus* carriage rates and methicillin-resistant *S. aureus* among health personnel by analyzing the relationship between carriage, individual risk factors and hand hygiene practices. Outcomes revealed a 20.1% prevalence of *S. aureus* carriage within 54 *S. aureus* carriers. Notably, *S. aureus* culture positivity exhibited a significant decrease in tandem with heightened handwashing frequency.[40] In this sense, health education is crucial to promote handwashing and support not only medical staff, but also patients to enhance hand hygiene frequency and technique.[15]

In the realm of research, the wide range of diseases linked to healthcare is acknowledged, particularly given the ongoing changes in hospital practices and the evolving nature of microbial behavior. This underscores the pressing need for a comprehensive review of the existing literature. As a consequence of this, the main objective of the present study was the identification of the predominant microbial strains, as well as the evaluation of their degree of resistance to antibiotics, specifically among the microorganisms present in the hands of healthcare personnel. The use of meta-analysis, in particular, is a fundamental methodological tool in this type of research. This technique enables the synthesis and analysis of data from multiple studies, which facilitates obtaining robust conclusions and making informed decisions in everyday clinical practice. The insights gained from this study are vital for reducing the risk of disease transmission within healthcare environments. This is advantageous for both patients and healthcare personnel, as the latter can act as active carriers of pathogens. However, certain limitations were noted; for example, studies included in the review may differ significantly in terms of sample collection methods, microbial identification techniques, and antimicrobial susceptibility testing. For example, some studies might use swabbing, others might use imprint methods, and the types of media or growth conditions can vary. Additionally, differences in defining and measuring outcomes, such as what constitutes "resistance" or "colonization" versus transient contamination, can vary. This variability can make it difficult to compare results across studies or aggregate data in a meaningful way. Other limitations are related to publication and reporting bias, as the detail in which methods and results are reported can vary, and some studies may not provide sufficient data on resistance mechanisms, or the specific microorganisms identified. This lack of detailed reporting can limit the ability to perform a thorough meta-analysis and may skew the understanding of the true scope of microbial resistance and susceptibility patterns on healthcare workers' hands. Finally, the resistance profiles of microorganisms can change over time due to factors such as the introduction of new antimicrobial agents or changes in infection control practices. Moreover, microbial flora and resistance patterns can vary significantly between different regions and healthcare settings. A systematic review and meta-analysis might aggregate data from different time periods and geographic locations, potentially obscuring important trends and making it difficult to draw specific, actionable conclusions for current practice in a particular setting.

CONCLUSION

Bacterial resistance and susceptibility pose a pervasive health hazard. Despite promising advancements in pharmacological research for prevention and treatment, governmental interventions and health researchers play pivotal roles in mitigating the adverse impact of bacteria on healthcare workers' hand hygiene. Conducting periodic bacterial population studies on healthcare workers individually is recommended to ascertain pathogen presence and distribution based on professional roles. Adherence to established clinical and surgical handwashing protocols is imperative, ensuring comprehensive technique assessment through implementation, monitoring, and enforcement if needed. Furthermore, broader studies encompassing bacterial resistance and susceptibility through meta-analyses are imperative. Such investigations guide decisions on managing pathogens prevalent on healthcare workers' hands, minimizing risks for personnel and surroundings. According to the Clinical Laboratory Standards Institute, doctors depend significantly on microbiology laboratories for patient care, highlighting the necessity for testing in well-equipped, modern laboratories. These facilities must adhere to current guidelines for drug selection, interpretation, and quality control, which aids in making informed assessments of bacterial resistance and susceptibility in the hand microbiomes of healthcare workers. Considering the limitations previously noted, certain measures could be implemented to enhance the results of the meta-analysis; for example, subgroup analyses to handle variations in study designs, techniques, and definitions could be implemented to reduce variability. This involves grouping studies by similar methods (e.g., type of microbial testing) or by healthcare settings (e.g., intensive care units vs. general wards). On the other hand, conducting sensitivity analyses to determine how the inclusion or exclusion of certain studies affects the results. This can help identify the impact of potentially biased studies. Finally, stratifying the results by different time periods and geographic regions can help to identify specific trends and differences in microbial resistance patterns over time or across locations. Although implementing these solutions requires meticulous planning and execution, it can significantly enhance the quality and applicability of a systematic review and meta-analysis in understanding microbial resistance on healthcare workers' hands.

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AUTHOR'S CONTRIBUTIONS

Nolbedir Saza Ramírez and **Fernando Rojas Páez** collected and analyzed data on the identification, resistance, and susceptibility of microorganisms on the hands of healthcare professionals. They also implemented the statistical analysis of the data. **Julieth Yadira Serrano Riaño** and **Juan Jairo Vaca-González** evaluated the collected data and analyzed the risk of bias in individual studies. All authors contributed to the study design, acquisition of data from medical science databases, classification of data using a checklist, analysis and interpretation of data, and interpretation, writing, and critical editing of the manuscript.

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