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

ISSN 2238-3360 | Ano XIII - Volume 13 - Número 1 - 2023

REVISTA DE EPIDEMIOLOGIA E CONTROLE DE INFECÇÃO

RECI

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

Revista de Epidemiologia e Controle de Infecção

Elaboração, veiculação e informações: *Núcleo de Epidemiologia do Hospital Santa Cruz*
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Veiculação: *Virtual*

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Revista de Epidemiologia e Controle de Infecção

Hospital Santa Cruz

R454 Revista de epidemiologia e controle de infecção [recurso eletrônico] / Núcleo Hospitalar de Epidemiologia do Hospital Santa Cruz, Programa de Pós Graduação em Promoção da Saúde.
Vol. 13, n. 1 (2023) Jan./Mar. - Santa Cruz do Sul: EDUNISC, 2023.

Dados eletrônicos.
Modo de acesso: World Wide Web: <*http://www.unisc.br/edunisc*>
Trimestral
eISSN 2238-3360

Temas: 1. Epidemiologia - Periódicos. 2. Microbiologia - Periódicos.
3. Doenças transmissíveis - Periódicos.
I. Núcleo Hospitalar de Epidemiologia do Hospital Santa Cruz. II. Título.

CDD: 614.405

Catalogação: Bibliotecária Jorcenita Alves Vieira CRB – 10/1319

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

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Revista de Epidemiologia e Controle de Infecção

Hospital Santa Cruz

ORIGINAL ARTICLE

Risk factors associated with surgical site infection in patients with musculoskeletal cancer

Fatores de risco associados à infecção de sítio cirúrgico em portadores de câncer musculoesquelético

Factores de riesgo asociados a la infección del sitio quirúrgico en pacientes con cáncer musculoesquelético

https://10.17058/reci.v13i1.17595

Received: *03/05/2022*
Accepted: *16/07/2022*
Available online: *06/03/2023*

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ABSTRACT

Background and objectives: surgical site infections (SSI) continue to be a major concern in orthopedic oncology and pose as great a challenge as cancer recurrence, despite the preventive potential of surgery. SSI can be avoided if evidence-based measures are taken. The objective was to assess the frequency of infections in oncological orthopedic surgeries and associated risk factors and inflammatory markers in a reference hospital in the state of Pernambuco. **Methods:** the frequency of SSI, the identification of isolated microorganisms, the risk factors and the profile of Th1 and Th2 inflammatory markers (IL-2, IL-4, IL-6, IL-10, TNF and IFN-Y) in patients with musculoskeletal cancer were analyzed. **Results:** SSI were found in 9.1% of patients undergoing orthopedic surgery. Bivariate analysis revealed that a surgical team comprising more than five members (p=0.041) and the need for intraoperative transfusion (p=0.012) were correlated with a higher risk of SSI. The measurement of ultrasensitive C-reactive protein levels to assess the inflammatory response after SSI showed results that were superior to the reference values for each sample, ranging from >5 to >200mg/dl by the immunoturbidimetric method. Of the IL-2, INFγ and TNF (Th1) and IL-4, IL-6, IL-10 (Th2) levels, only interleukin 6 showed high levels, between 6.68 and 58.76 pg/mL. **Conclusion:** the study found that surgical team with five or more members and blood transfusion were factors associated with the development of SSI in orthopedic surgery in patients with musculoskeletal cancer. Among the inflammatory markers, interleukin 6 (IL-6) showed the highest correlation with the outcome.

Keywords: *Surgical Site Infection. Risk Score. Orthopedics. Cancer.*

RESUMO

Justificativa e objetivos: as infecções do sítio cirúrgico (ISC) continuam sendo uma grande preocupação na oncologia ortopédica e representam um desafio tão grande quanto a recorrência do câncer, apesar do potencial

Please cite this article as: *Bezerra da Silva , G. G. ., Palmares Oliveira e Silva , M. ., Barros Lorena, V. M. . ., Pedrosa Soares, C. R., & Ramos de Araújo , P. S. . (2023). Fatores de risco associados à infecção de sítio cirúrgico em portadores de câncer musculoesquelético. Revista De Epidemiologia E Controle De Infecção, 13(1). https://doi.org/10.17058/reci.v13i1.17595*

preventivo da cirurgia. As ISC podem ser evitadas se forem tomadas medidas baseadas em evidências. O objetivo foi avaliar a frequência de infecções em cirurgias ortopédicas oncológicas e os fatores de risco e marcadores inflamatórios associados em um hospital de referência no estado de Pernambuco. **Métodos:** foram analisados a frequência de ISC, a identificação de microrganismos isolados, os fatores de risco e o perfil de marcadores inflamatórios Th1 e Th2 (IL-2, IL-4, IL-6, IL-10, TNF e IFN-Y) em pacientes portadores de câncer musculoesquelético. **Resultados:** as ISC foram encontradas em 9,1% dos pacientes submetidos à cirurgia ortopédica. A análise bivariada revelou que uma equipe cirúrgica composta por mais de cinco membros (p=0,041) e a necessidade de transfusão intraoperatória (p=0,012) foram correlacionadas com maior risco de ISC. A dosagem dos níveis de proteína C reativa ultrassensível para avaliação da resposta inflamatória após ISC apresentou resultados superiores aos valores de referência para cada amostra, variando de >5 a >200mg/dl pelo método imunoturbidimétrico. Dos níveis de IL-2, INFγ e TNF (Th1) e IL-4, IL-6, IL-10 (Th2), apenas a interleucina 6 apresentou níveis elevados, entre 6,68 e 58,76 pg/mL. **Conclusão:** o estudo constatou que equipe cirúrgica com cinco ou mais membros e transfusão sanguínea foram fatores associados ao desenvolvimento de ISC em cirurgia ortopédica em pacientes com câncer musculoesquelético. Entre os marcadores inflamatórios, interleucina 6 (IL-6) apresentou maior correlação com o desfecho.

Palavras-chave: *Infecção de Sítio Operatório. Pontuação de Risco. Ortopedia. Câncer.*

RESUMEN

Justificación y objetivos: las infecciones del sitio quirúrgico (ISQ) siguen siendo una preocupación importante en la oncología ortopédica y representan un desafío tan grande como la recurrencia del cáncer, a pesar del potencial preventivo de la cirugía. Las ISQ se pueden prevenir si se toman medidas basadas en la evidencia. El objetivo fue evaluar la frecuencia de infecciones en cirugías ortopédicas oncológicas y los factores de riesgo y marcadores inflamatorios asociados en un hospital de referencia en el estado de Pernambuco. **Métodos:** se analizaron la frecuencia de ISQ, la identificación de microorganismos aislados, los factores de riesgo y el perfil de marcadores inflamatorios Th1 y Th2 (IL-2, IL-4, IL-6, IL-10, TNF e IFN-Y) en pacientes con cáncer musculoesquelético. **Resultados:** se encontraron ISQ en el 9,1% de los pacientes sometidos a cirugía ortopédica. El análisis bivariado reveló que un equipo quirúrgico compuesto por más de cinco miembros (p=0,041) y la necesidad de transfusión intraoperatoria (p=0,012) se correlacionaron con un mayor riesgo de ISQ. La medición de los niveles de proteína C reactiva ultrasensible para evaluar la respuesta inflamatoria después de la ISQ presentó resultados superiores a los valores de referencia para cada muestra, variando de >5 a >200 mg/dl por el método inmunoturbidimétrico. De los niveles de IL-2, INFγ y TNF (Th1) e IL-4, IL-6, IL-10 (Th2), solo la interleucina 6 mostró niveles elevados, entre 6,68 y 58,76 pg/mL. **Conclusión:** el estudio encontró que el equipo quirúrgico con cinco o más miembros y la transfusión el estudio encontró que un equipo quirúrgico con cinco o más miembros y transfusión de sangre fueron factores asociados con el desarrollo de ISQ en cirugía ortopédica en pacientes con cáncer musculoesquelético. Entre los marcadores inflamatorios, la interleucina 6 (IL-6) mostró la mayor correlación con el resultado.

Palabras clave*: Infección del Sitio Quirúrgico. Puntuación de Riesgo. Ortopedía. Cáncer.*

INTRODUCTION

In recent years, the number of surgical interventions to treat cancer has increased throughout the world, reflecting a worldwide increase in the incidence of malignant neoplasias.[1] It is estimated that there will be 625,000 new cases of cancer in the three-year period between 2020 and 2022 in Brazil.[2] Despite the development of less invasive treatment involving medication, surgery remains a fundamental tool in treatment of musculoskeletal cancer.[3]

Surgery is a treatment method of great importance for patients, as it plays a fundamental role in loco-regional control of the disease and in establishing the parameters of the recommended cancer treatment. Surgical site infections (SSI) have been shown to be the most common complication during treatment.[4]

Despite the significant preventive potential of surgery, it is important that SSI are avoided, given that such infections continue to be a major concern in orthopedic oncology and represent a challenge as great as cancer recurrence, with an incidence between 3, 2 and 35.55%. [1,5,6]

The risk of infection may lead to devastating musculoskeletal complications, requiring bone resection and prosthetic use.[4] This complication may also result in physical, social and/or psychological damage to patients, along with longer stays in hospital, increased risk of re-hospitalization, the need for further surgery, the persistence of painful symptoms, the need for antibiotics, possible loss of implants, limb amputation, infections and death [7] thus substantially increase the cost of treatment.[8]

Numerous factors have been associated with the development of SSI. These risk factors are commonly divided into modifiable and non-modifiable factors. Potentially modifiable factors include a pre-operative antiseptic bath in the case of major surgery and/or implant insertion, routine hair removal discontinuation, hospitalization length of less than 24 hours, blood sugar level control immediately prior to and following surgery,

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smoking, recent history of immunosuppression, obesity and effective infusion of prophylactic antibiotics for up to 60 minutes prior to surgical incision. Non-modifiable factors include advanced age, history of prior infections, and advanced-stage cancer. SSI also tend to be associated with emergency surgery, lengthy surgery, surgery involving large teams, blood transfusion, an skin antisepsis quality in patients and hand hygiene among the care team.[9,10]

Numerous inflammatory markers have been proposed for infection identification, including high-sensitivity and -specificity cytokines, which are considered to be important mediators in the host's response to infection and C-reactive protein levels and are thus used for early identification of infection, along with clinical evaluation and other laboratory examinations.[11]

Considering the greater complexity of the disease, SSI in patients with bone cancer deserve more extensive studies in the scientific community. In addition to the underlying disease-related disorders, the aggressive nature of cancer treatment causes significant immune imbalance, increasing the risk of infection during surgery. Moreover, treating the infection can, in turn, delay or even prevent cancer treatment.[1,7]

The objective was to assess the frequency of infections in oncological orthopedic surgeries and the associated risk factors and inflammatory markers in a reference hospital in the state of Pernambuco.

METHODS

An observational, analytical, cross-sectional study was carried out with 110 individuals of both sexes, of any age, diagnosed with primary or secondary bone cancer and confirmed by histopathological examination and undergoing orthopedic surgery, between July 2019 and July 2020, at the *Hospital de Câncer de Pernambuco*, in Recife, Brazil. Individuals who, upon hospital admission, had skin/soft tissue infection in the topography of the limb to be surgically treated and individuals with benign tumors were excluded. Written consent was obtained from participants through the Informed Consent Form, for cases over 18 years of age, and the Clarified Assent Form, for those under 18 years of age. The study was approved by the Research Ethics Committee of the *Hospital de Cancer de Pernambuco*, CAAE (13514019.2.0000.5205) ethics opinion (3.399.327) in accordance with Resolution 466/12 of the Brazilian National Health Council (CNS).

The collection of clinical and epidemiological, sociodemographic data, such as lifestyle, tobacco use, Body Mass Index (BMI), immunosuppressant use in the last six months, bacterial infection in the last 30 days, presence of SSI, cancer type and cancer site, preoperative hospital stay, surgery duration, antibiotic prophylaxis, preoperative bath, glycemic control, preoperative shaving, degree of contamination, implant insertion, number of surgery participants ≥5, blood transfusion, was extracted from patients' records. Blood samples were collected to assess inflammatory markers. We found the frequency of SSI, identification of microorganisms isolated in blood samples in SSI, risk factors and profile of Th1 and Th2 inflammatory markers (IL-2, IL-4, IL-6, IL-10, TNF and IFN-Y) using the flow cytometry technique up to 48 hours after the diagnosis of SSI using the SPSS (Statistical Package for the Social Sciences), version 21.0 (IBM, Armonk, NY). After diagnosis of SSI in accordance with the criteria of the Brazilian National Healthcare Safety Network, the Centers for Disease Control and Prevention and the Brazilian Health Regulatory Agency (ANVISA - *Agência Nacional de Vigilância Sanitária*), blood samples were collected, centrifuged and stored at -20°C, and then sent to the Marcelo Magalhães Laboratory, for measuring ultrasensitive C-reactive protein levels using the immunoturbidimetric method, and to the Department of Immunology at the *Instituto Aggeu Magalhães*/FIOCRUZ, to ascertain the IL-2, INFγ and TNF (Th1) and IL-4, IL-6, IL-10 (Th2) cytokine profile by way of flow cytometry using the Cytometric Bead Array (CBA) method.

Clinical data on patients' lifestyle and previous and current medical history included smoking, BMI, immunosuppressant use in the past six months, bacterial infection in the last 30 days, and type and location of cancer. The variables relating to the healthcare process were length of hospital stay prior to surgery, surgery duration, antibiotic prophylaxis, preoperative bath, blood sugar control, hair removal prior to surgery, contamination level, implant insertion, number of team members participating in surgery ≥5, and blood transfusion. Preoperative, transoperative and postoperative variables for patients with a diagnosis of bone cancer following histopathological examination were taken from medical records in the first 24 hours after surgery.

Sample analysis

Identification of micro-organisms was carried out at the study location using an automated method called VITEK® 2 (*bioMérieux Brasil*) for analyzing samples of tissue fragment culture following diagnosis of SSI and duly recorded. C-reactive protein was measured using the immunoturbidimetric latex agglutination method in serum, and the result for C-reactive protein (CRP) concentration in the sample was read using a spectrophotometer. The benchmark value for the laboratory was considered to be 0-5mg/L.

Cytokine examination was carried out using a CBA (BD) kit for quantification of IL-2, INFγ and TNF (Th1) and IL-4, IL-6, IL-10 (Th2) cytokines in a single sample. Six populations of beads with distinct fluorescence intensities were associated with a capture antibody specific to each cytokine, mixed to form CBA and read using the FL3 channel of a FACScalibur (BD) flow cytometer. The populations of beads were viewed using their respective fluorescence intensities: from brightest to least bright. In CBA, cytokine capture beads are mixed with the detection antibody conjugated to phycoerythrin (PE) fluorochrome, and then incubated together with the samples to form a "sandwich assay". Acquisition tubes were prepared with 50 µL of sample, 50 µL of bead mixture and 50 µL Th1/Th2 PE detection reagent (Human Th1/Th2 PE Detection Reagent/1 vial, 4 mL). The same procedure was

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performed to obtain the standard curve. The tubes were homogenized and incubated for three hours, at room temperature, in the dark. The flow cytometer was calibrated and its channels/filters adjusted prior to sample collection. The standard curve was obtained, using the same kit, subsequent to sample collection. The results were presented in the form of graphs and tables using FCAP Array™ v3.

Statistical analysis

Frequency comparison of SSI involving qualitative variables were carried out using Pearson's chi-squared test or Fisher's exact test, as appropriate. For quantitative variables, non-parametric Mann-Whitney or Student's t test were used, for non-normal or normally distributed data, respectively. The significance level was set at 5%. Statistical analysis was carried out using SPSS, version 21.0 (IBM, Armonk, NY). The SPSS program (IBM SPSS Statistics 24) was used to calculate the sample size, and the sample was calculated with a 5% sampling error, 95% Confidence Interval and 80% test power, using a population prevalence of 154 individuals, thus obtaining a total of 110 samples. Multivariate analysis was carried out using logistic regression, which enables simultaneous assessment of all the effects, taking SSI to be a dependent variable. Independent variables were included in the regression if they presented a p-value < 0.20 on bivariate analysis (age, length of hospital stay, hair removal, pelvic surgery, number of participants in surgery equal to or greater than five and need for intra-operative transfusion). Variables were selected using the stepwise forward method, with a significance level of 0.05 for inclusion of variables, and 0.10, for removal.

RESULTS

During the study period, 110 patients undergoing orthopedic surgical procedures diagnosed with bone cancer were recruited. Of this total, 10/110 (9.1%) had SSI. Most patients were female, five with SSI and 54 without SSI (59%), and the mean age was 31 years of age for patients with SSI and 26 years of age for patients without SSI (Table 1).

Table 1. Distribution of orthopedic oncology surgery patients by age and sex.

Characteristic	SSI				
	Yes (n=10)		Yes (n=10)		p-value
Gender	**N**	**%**	**N**	**%**	1.00
Female	5	50	54	54	
Male	5	50	46	46	
Age					0.163$_t$
Mean (SD)	31 (21 – 34)		26 (21 – 32)		

Caption: SD = standard deviation; t = Student's t test

With regard to the previous and current medical history of patients developing SSI, the most frequent type of musculoskeletal cancer was sarcoma (7/10; 70%) in SSI, and 53/100 (53%) individuals did not have SSI, which is considered to be the most prevalent type of tumor in the population under study. The tumor was mostly located in the pelvis or upper limbs (10/10; 100%) in SSI, and 70/100 (70%) individuals did not have SSI, which also reflected the prevalence in the sample as a whole (Table 2).

With regard to lifestyle, (10/100) 10% of individuals included in the sample were current smokers, although none of these developed an SSI. The mean BMI exceeded 25 in 60% of the group of patients who developed SSI. The mean BMI was similar between the SSI and non-SSI groups. Immunosuppressant use <6 months was more frequent in individuals with SSI (1/10; 10%), and the presence of bacterial infection <4 months was 1/10 (10%) in patients with SSI and 97/100 (97%) in patients without SSI. None of these variables were statistically significant (Table 2).

Table 2. Lifestyle and past and current medical history of orthopedic oncology surgery patients.

Biological Characteristics	SSI				
	Yes (n=10)		Yes (n=10)		p-value
Smoking	**N**	**%**	**N**	**%**	0.735
Yes	0	0	10	10	
No	10	100	90	90	
BMI					0.733t
Mean (SD)	25 (5.7)		25,5 (4.5)		
Immunosuppressant use <6 months					0.201
Yes	1	10	2	2	
No	9	90	98	98	
Bacterial infection <4 months					0.329
Yes	1	10	97	97	
No	9	90	3	3	
Leukocytes					0.650MW
Median	7515		7450		
(P25 – P75)	(6942– 5775)		(6200–9495)		
Cancer type					0.629
Sarcoma	7	70	53	53	
Chondrosarcoma	1	10	10	10	
Other	2	20	37	37	
Cancer site					0.215
Head/neck	0	0	1	1	
Trunk/upper limbs	0	0	29	29	
Pelvis/lower limbs	10	100	70	70	

Caption: SD = standard deviation; P25 = 25th percentile; P75 = 75th percentile 75; MW = Mann-Whitney test; t= Student's t test.

With regard to healthcare-related variables, all surgical procedures were elective, and most were classified as clean (10/10; 100%) in patients with SSI, and 97/100 (97%) patients did not have SSI, with hospital stay before surgery longer than 24 hours in 60% of patients who developed SSI and mean surgery duration from 61 to 120 minutes, with surgery performed by a care team of five or more participants in 80% of cases that developed ISC. Blood glucose was controlled in 3/100 (2.72%) patients without SSI. None of the surgical procedures were prece-

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ded by an antiseptic bath and all involved administration of the recommended prophylactic antibiotic, with no available record of duration of administration. Forty percent 4/10 of patients who received an orthopedic implant during surgery developed SSI (Table 3).

Bivariate analysis showed that a number of team members actively participating in the surgery equal to or greater than five (Odds Ratio [OR] 5.524; Confidence Interval [95%CI] 1.116 – 27.348; p = 0.041) and the need for intraoperative transfusion (OR 7.667; 95%CI 1.786 – 32.910; p = 0.012) suggested an association with SSI. The other independent variables had no significant effect on the risk of developing SSI (Table 3).

Table 3. Healthcare process indicators of orthopedic oncology surgery patients.

Indicators	**SSI**				
	Yes (n=10)		**Yes (n=10)**		**p-value**
Length of hospital stay prior to surgery	**N**	**%**	**N**	**%**	0.165
≤ 24 h	4	40	66	66	
> 24 h	6	60	34	34	
Surgery duration (hours)					0.143_{MW}
Median (P25 – P75)	1.50 (1.50-2.50)		1.25 (1.25-2.25)		
Blood sugar control					1.00
Yes	0	0	3	2.72	
No	10	100	97	97.28	
Hair removal prior to surgery					0.174
Yes	1	10	1	1	
No	9	90	99	99	
Contamination status					0.857
Clean	10	100	97	97	
Potentially contaminated	0	0	1	1	
Contaminated	0	0	2	2	
Implant insertion					0.456
Yes	4	40	26	26	
No	6	60	74	74	
Number of team members in room ≥5					0.041
Yes	8	80	42	42	
No	2	20	58	58	
Blood transfusion					0.012
Yes	4	40	6	60	
No	6	60	94	94	

Caption: P25 = 25th Percentile; P75 = 75th Percentile; MW = Mann-Whitney test.

Factors with p-value <0.20 in univariate analysis included in multiple logistic regression were age, length of hospital stay, hair removal, pelvic surgery, number of team members who participated in the surgery ≥5 and intraoperative blood transfusion. The variables were selected using the forward stepwise method, with a significance level of 0.05 for inclusion of variables and of 0.10 for removal. Multivariate analysis revealed that the need for intra-operative transfusion (OR 8.22; 95%CI 1.81-27.37; p = 0.006) was the only risk factor for developing SSI.

Outcomes for patients with surgical site infection

According to the classification of infections, all were classified as deep. Patients who developed SSI needed to be admitted to hospital again and underwent further surgery, most of them one or two further procedures, three of these involving amputation of the infected limb. The micro-organism most commonly found in cases with a positive culture was *Staphylococcus aureus*, identified in 50%. In two of these ten patients, the surgeon identified signs and symptoms of purulent secretion, indicating infection at the site of surgery despite a negative culture in accordance with the criteria of the National Health Security Network of the Centers for Disease Control and Prevention. The mean length of hospital stay after diagnosis of infection was 11 to 20 days, and 50% of patients required intensive care. No SSI-related deaths were recorded among these patients. Three patients with SSI underwent amputation. During the study, none of these patients with SSI died (Table 4).

Table 4. Characterization of SSI orthopedic oncology surgery patients.

	SSI N=10	
Clinical characteristics	**N**	**(%)**
Classification of SSI		
Superficial	0	0
Deep	10	100
Organ space	0	0
Culture collected		
Yes	8	80
No	2	20
Micro-organism isolated		
Staphylococcus aureus	5	50.0
Klebsiella pneumoniae	2	20.0
Pseudomonas aeruginosa	1	10.0
Negative culture	2	20.0
Retreatment		
Yes	10	100
No	0	0
Number of retreatments		
1-2	7	70
3-4	2	20
≥5	1	10
Length of hospital stay subsequent to SSI		
≤10 days	2	20
11-20 days	5	50
21-30 days	3	30
>30 days	0	0
Need for transfer to ICU		
Yes	5	50
No	5	50
Amputation		
Yes	3	30
No	7	70
Death		
Yes	0	0
No	10	100

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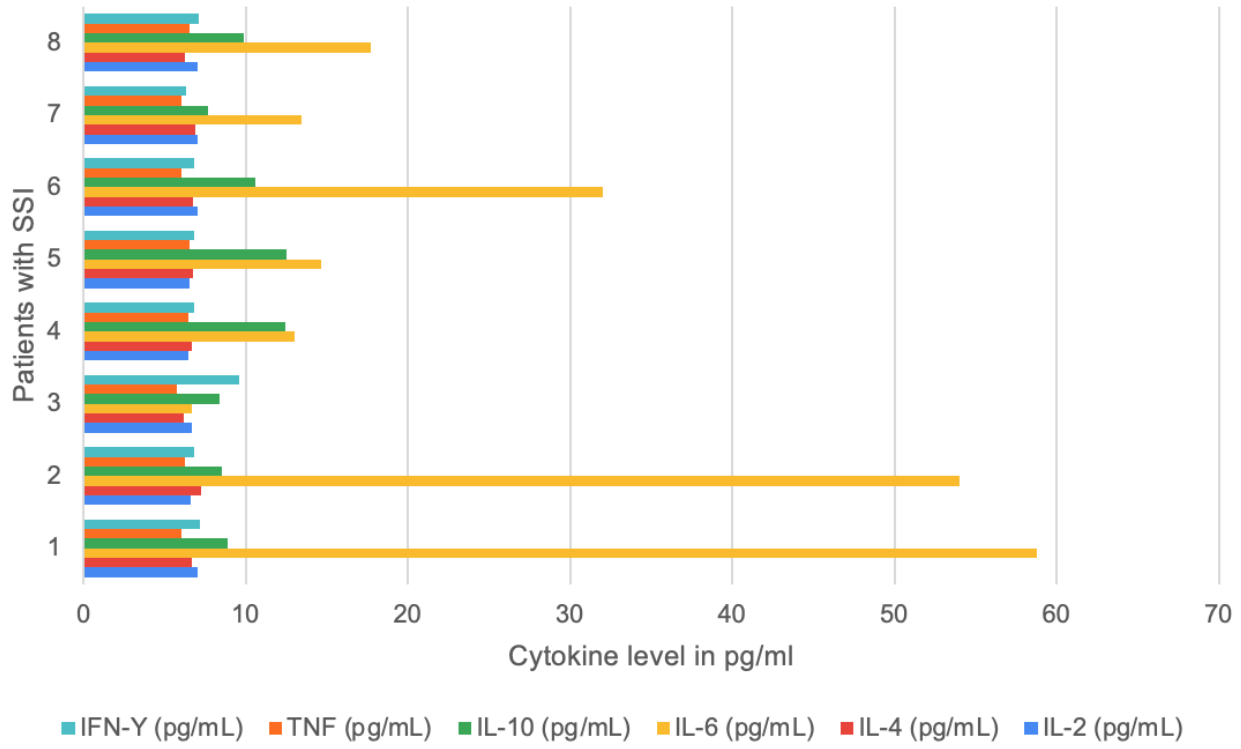

Figure 1. Distribution of cytokine levels measured in pg/ml using the Cytometric Bead Array method.

Inflammatory markers

Ultrasensitive CRP levels, used to assess the immune response after SSI, were >5 mg/dl in 100% of the samples analyzed. Four patients had CRP between 5-25 mg/L (44.44%); two patients had CRP between 26-100mg/L (22.22%); two had CRP between 100-200mg/L (22.22%); and one patient had CRP above 200 mg/L (11.11%).

With regard to cytokines, interleukin 6 (IL-6) presented the highest levels, between 6.68 and 58.76pg/mL. The others did not show any significant variations (Figure 1).

DISCUSSION

The results of this study indicate an incidence of infection of 9.09%, a similar value reported in a study of risk factors for SSI in orthopedic oncology that found that 10.9% of patients developed SSI.[5] On the other hand, the incidence of postoperative infection of deep bone tumors ranged from 3.2% to 10.9%.[1,6] All the procedures included in the study were classified as clean and the incidence of SSI for this category of procedure was higher than the rate considered acceptable (1 to 5%).[9]

The present study found that most cases of SSI involved patients aged over 55 years,[10] who considered belonging to this age group a significant risk factor for SSI, along with overweight and obesity. It also reported obesity to be an independent risk factor for SSI (OR: 1.43; 95%CI: 1.13-2.00) in a study of patients undergoing internal fixation of calcaneal fractures.[12]

The present study also identified that patients receiving a blood transfusion for volume loss were around eight times more likely to have an SSI (OR 8.22; 95%CI 1.81-27.37; p = 0.006) compared to patients with no volume loss. Patients who receive perioperative blood transfusion are at increased risk of developing SSI.[13] In a cohort study with 222 patients undergoing orthopedic surgery with implants, in which those who received perioperative blood transfusion had a three times greater risk of developing SSI compared to the group not submitted to blood transfusion (HR: 3.08; 95%CI: 1.31-7.26,).[8] These findings are supported by a study that found that blood transfusion is a risk factor for developing SSI, being 2.6 times more likely to develop an infection compared to those who did not receive a blood transfusion, in addition to having a longer hospital stay.[14]

The number of colony forming units (CFU) collected in sterile containers in the operating room through microbiological analysis was not significantly associated with the number of individuals in the room.[15] However, the presence of five or more members of the care team at surgery has been an independent risk factor for SSI.[16]

Studies show that implant use in orthopedic oncologic surgery has increased the likelihood of deep infection.[1] General procedures associated with orthopedic diagnosis and treatment, implantation or removal of a musculoskeletal device had the highest prevalence of infections related to implantable orthopedic devices.[17] The study found that 40% of surgeries that led to infection involved the insertion of an implant.

Please cite this article as: *Bezerra da Silva , G. G. ., Palmares Oliveira e Silva , M. ., Barros Lorena, V. M. . ., Pedrosa Soares, C. R., & Ramos de Araújo , P. S. . (2023). Fatores de risco associados à infecção de sítio cirúrgico em portadores de câncer musculoesquelético. Revista De Epidemiologia E Controle De Infecção, 13(1). https://doi.org/10.17058/reci.v13i1.17595*

Smokers are about 6.4 times more likely to develop SSI than non-smokers,[18] despite the fact that in this study none of the patients with SSI reported being a smoker. No patient who developed SSI had a previous or concomitant infection.

Studies show that patients undergoing bone tumor resection at any site followed by reconstruction are risk factors for SSI.[6] Our findings indicate that all infections occurred after surgical interventions involving tumors in the lower limbs and pelvis.

In the present study, length of hospital stay before surgery was greater than 24 hours in 60% of SSI cases, although this number was not statistically significant. Musculoskeletal tumor patients undergoing surgery were at higher risk for SSI.[19]

Surgery duration has been considered an independent risk factor for deep wound infection.[20] The present study found that the mean surgery duration ranged from 85 to 90 minutes, although it was not a risk factor for infections in cancer patients.

Hyperglycemia was associated with a higher incidence of SSI.[21] This study showed the absence of glycemic control in 97.27% of the total sample and 100% of the SSI group.

SSI prevention through an antiseptic bath before major surgeries or implants was not performed in any of the patients, and this can be explained by the lack of an effective protocol at the institution. It was therefore not possible to investigate the effectiveness of this measure.

With regard to prophylactic antibiotics, it is stated in the literature that antibiotic infusion should occur up to 60 minutes prior to surgical incision, in order to ensure serum concentrations sufficient to prevent SSI [1], although no reports of this time being abided by were found in the research.

The microorganism most commonly involved in orthopedic SSI is *Staphylococcus aureus*. The same conclusion was made about infections in orthopedic surgery published between 2015 and 2020.[22] This is corroborated by the findings of the present study.

We found that all patients with SSI were reoperated on and re-hospitalized, requiring intensive care in the most severe cases.

The CRP level, when used with other clinical interventions, has been highly effective in diagnosing SSI and can be used as a criterion to select patients who may need an invasive intervention due to infectious complications,[23] showing a sustained increase in protein levels in cases of postoperative infection. In our study, postoperative levels exceeded the reference level (>5 mg/dl) in all samples.

For cytokines, the study showed that interleukin 6 occurred at high levels in 87.5% of the measured samples. Inflammatory markers such as CRP and IL-6 in lesion fluid hold promise for predicting SSI in the clinic.[24] Serial estimation of postoperative CRP and IL 6 can predict infections and can be used routinely in general surgical practice.[25]

It is not possible to generalize the study findings to other individuals due to the underlying disease character of the population studied. The larger sample size could contribute to a better understanding of the associations studied.

The study found that surgical team with five or more members and blood transfusion were risk factors associated with the development of SSI in orthopedic surgery in patients with bone cancer. Among the inflammatory markers, interleukin 6 (IL-6) showed the highest correlation with the outcome. More studies are needed to determine the degree of modulation of inflammatory responses in this population. Patients who develop SSI require longer hospital stays for adjuvant therapy involving antibiotics and reoperation for infection control and, in some cases, involving amputation.

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AUTHORS' CONTRIBUTIONS:

Each author has made a significant individual contribution to the production of this article. **Gerlany Gisely Bezerra da Silva** was responsible for writing the article, collecting clinical data from medical records and performing immunological tests; **Marcelo Palmares Oliveira e Silva** analyzed the data and performed laboratory tests; **Virgínia Maria Barros Lorena** analyzed the data and made a critical review of the article's content; **Cynthia Regina Pedrosa Soares** and **Paulo Sergio Ramos de Araújo** reviewed and approved the article and were responsible for the study design.

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

Revista de Epidemiologia e Controle de Infecção

Hospital Santa Cruz

ORIGINAL ARTICLE

Gestational syphilis at different health care levels: a cross-sectional study

Sífilis gestacional em diferentes níveis de atenção à saúde: um estudo transversal

Sífilis gestacional en diferentes niveles de atención de salud: un estudio transversal

https://doi.org/10.17058/reci.v13i1.17722

Received: *06/14/2022*
Accepted: *10/08/2022*
Available online: *06/03/2023*

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ABSTRACT

Background and objectives: Syphilis is a sexually transmitted disease that can cause miscarriage, premature birth, malformations, and neonatal death. When diagnosed and treated in the first months of pregnancy, the neonatal risks are considerably reduced. This work aims to discuss the key points regarding prevention and effective treatment of gestational syphilis at different health care levels. **Methods:** Retrospective cross-sectional study. A survey was carried out about syphilis notifications recorded at a hospital in Porto Alegre, RS, from January to June 2021, considering the variables date of diagnosis and notification and laboratory, treatment, and prenatal care data collected in hospital records and the e-SUS system. **Results:** In the study period, 17 cases of gestational syphilis and 102 cases in newborns were notified. We selected the case of a patient with a history of two pregnancies without prenatal care and use of psychoactive substances. This case illustrates the patient's itinerary in Primary Care, in specialized services such as the Center for Psychosocial Care and High-Risk Prenatal Care, and hospital care, showing the availability of care and, at the same time, the fragmentation of services. **Conclusion:** Multidisciplinary actions are needed at different health care levels to ensure access to testing for pregnant women and their partners, family planning, and adequate syphilis treatment, which interrupts the disease transmission chain and avoids possible complications of neonatal syphilis.

Keywords: *Syphilis. Syphilis, Congenital. Comprehensive Health Care. Maternal-Child Health Services.*

RESUMO

Justificativa e objetivos: A sífilis é uma infecção sexualmente transmissível que pode causar aborto, parto prematuro, malformações e morte neonatal. Quando diagnosticada e tratada nos primeiros meses da gestação, os riscos neonatais são consideravelmente diminuídos. Este trabalho tem como objetivo discutir os pontos-chave na prevenção e no tratamento efetivo da sífilis gestacional no contexto dos diferentes níveis de atenção à saúde. **Métodos:** Estudo transversal retrospectivo. Foi realizado um levantamento das notificações de sífilis em um hospital

de Porto Alegre, RS, de janeiro a junho de 2021, considerando as variáveis data do diagnóstico e da notificação e dados de exames laboratoriais, de tratamento e de atendimento pré-natal, coletadas nos registros hospitalares e no sistema e-SUS. **Resultados:** No período do estudo, foram notificados dezessete casos de sífilis em gestantes e 102 em recém-nascidos. Selecionamos o caso de uma paciente com histórico de duas gestações sem pré-natal e uso de substâncias psicoativas. O caso ilustra o itinerário da paciente na atenção primária, em serviços especializados, como Centro de Atenção Psicossocial e Pré-Natal de Alto Risco, além do atendimento hospitalar, demonstrando a disponibilidade dos atendimentos e, ao mesmo tempo, a fragmentação dos serviços. **Conclusão:** São necessárias ações multidisciplinares nos diferentes níveis de atenção à saúde para garantir acesso à testagem da gestante e seus parceiros, ao planejamento familiar e ao tratamento adequado da sífilis, que interrompa a cadeia de transmissão da doença e evite possíveis complicações da sífilis neonatal.

Descritores: *Sífilis. Sífilis Congênita. Assistência Integral à Saúde. Serviços de Saúde Materno-Infantil.*

RESUMEN

Justificación y objetivos: La sífilis es una infección de transmisión sexual que puede causar aborto espontáneo, parto prematuro, malformaciones y muerte neonatal. Su diagnóstico y tratamiento en los primeros meses de embarazo lleva a una considerable reducción en los riegos neonatales. Este trabajo tiene como objetivo discutir los puntos clave en la prevención y tratamiento efectivo de la sífilis gestacional en el contexto de los diferentes niveles de atención a la salud. **Métodos:** Estudio transversal retrospectivo. Se realizó una encuesta de notificaciones de sífilis en un hospital de Porto Alegre (Brasil), de enero a junio de 2021, considerando las siguientes variables fecha de atención y notificación, y datos de exámenes de laboratorio, de tratamiento y control prenatal, recabadas de los registros hospitalarios y del sistema e-SUS. **Resultados:** Durante el período de estudio se reportaron diecisiete casos de sífilis en embarazadas y 102 en recién nacidos. Seleccionamos el caso de una paciente con antecedentes de dos embarazos sin control prenatal y consumo de sustancias psicoactivas. El caso ilustra el itinerario de la paciente por la atención primaria, por servicios especializados como el Centro de Atención Psicosocial y Atención Prenatal de Alto Riesgo, además de la atención hospitalaria, lo que demostró la disponibilidad de la atención y, al mismo tiempo, la fragmentación de los servicios. **Conclusiones:** Son necesarias acciones multidisciplinarias en los diferentes niveles de atención a la salud para garantizar el acceso a la prueba de la embarazada y de sus parejas, a la planificación familiar y al tratamiento adecuado de la sífilis, lo que interrumpa la cadena de transmisión de la enfermedad y evite posibles complicaciones de la sífilis neonatal.

Palabras clave: *Sífilis. Sífilis Congénita. Atención Integral de Salud. Servicios de Salud Materno-Infantil.*

INTRODUCTION

Syphilis is an infectious disease caused by the bacterium *Treponema pallidum*, from the group of spirochetes, which can be transmitted both sexually (acquired syphilis) and vertically in contact during pregnancy (congenital syphilis), and can reach 40% of fetal mortality.[1,2] According to data from the World Health Organization (WHO), most women with syphilis (about 80%) are of reproductive age, a factor that increases the risk of vertical transmission. In Brazil, the incidence is approximately 4% in the general population and 2% in pregnant women, with a higher rate of transmission in the early stages of the disease. In pregnant women, vertical transmission to the fetus can reach 80% intrauterine and can also occur during vaginal delivery if the mother has any injury due to syphilis.[1,3]

The burden of morbidity and mortality due to congenital syphilis is high, and most untreated infections due to syphilis during pregnancy result in adverse outcomes. In 2012, the estimate was 143,000 fetal deaths/stillbirths, 62,000 neonatal deaths, 44,000 premature or low birth weight babies, and 102,000 infected babies. These outcomes can be avoided if the pregnant woman receives appropriate treatment, preferably during the first trimester of pregnancy.[3] Diagnosis and treatment, even in asymptomatic cases, are important due to the possibility of reinfection, in addition to the possibility of disease progression in the absence of adequate treatment.[4]

About 60% to 90% of newborns with congenital syphilis are asymptomatic at birth. The presence of signs and symptoms at birth depends on the time of intrauterine infection and treatment during pregnancy, thus, serological screening and appropriate treatment of pregnant women and partners from prenatal care are essential. Prematurity and low birth weight are frequent perinatal complications. Frequent manifestations of early congenital syphilis (before 2 years of age) are: hepatomegaly, splenomegaly, jaundice, serosanguineous rhinitis, maculopapular rashes, bone abnormalities, thrombocytopenia, and anemia. The clinical manifestations of late congenital syphilis may involve developmental delay, neurological deafness, short jaw, and seizures, which appear in approximately 40% of infected and untreated children in the first months of life.[5]

Every pregnant woman should be tested for syphilis at least twice during prenatal care, once in the first

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trimester of pregnancy and once in the third trimester, the partner should also be tested. A third test should also be performed at the time of admission to the maternity ward, including for other sexually transmitted infections (STIs).[1] Also, investigating syphilis immediately after hospitalization for delivery in the maternity ward, or in case of abortion, is also mandatory.[6]

The diagnosis of syphilis occurs from clinical data, results of diagnostic tests, history of past infections, and investigation of recent exposure.[6] The easiest way to access it is the rapid treponemal test, which is available in Primary Health Care (PHC) and in maternity hospitals, aiming to expedite the diagnosis, since the time between the execution and the result is a maximum of 30 minutes, with sensitivity of 94.5% and specificity of 93%.[6]

To treat congenital syphilis, according to the Clinical Protocol and Therapeutic Guidelines for Integral Care to People with Sexually Transmitted Infections (PCDT-IST),[1] the treatment or not of the mother during pregnancy and the titration of the mother's non-treponemal test compared with that of the child is considered.

Children with congenital syphilis should be treated with crystalline benzylpenicillin in a hospital setting, with clinical and laboratory follow-up. In cases of children born to mothers who did not undergo any treatment or underwent inadequate treatment during pregnancy but have normal physical and behavioral examination and non-reactive treponemal test, treatment is performed with benzathine benzylpenicillin in a single dose. The exception of drug treatment occurs when the child is born to a mother who underwent adequate treatment during pregnancy, before the fifth month of gestation and has a non-reactive non-treponemal test. In this case, the child is not notified and follows up with the PHC, with laboratory follow-up for monitoring.[1]

According to data from the Ministry of Health, in 2021, 74,095 cases of syphilis in pregnant women (incidence coefficient of 27.1 per 100,000/inhabitants) and 27,019 cases of congenital syphilis (incidence coefficient of 9.9 per 100,000/inhabitants) were reported in Brazil. In Rio Grande do Sul, the incidence coefficient of syphilis in pregnant women was 38.1 per 100,000/inhabitants, and the incidence coefficient of congenital syphilis was 15.8 cases per thousand live births.[7]

In 2020, 115,371 cases of acquired syphilis (detection rate of 54.5 cases/100,000 inhabitants); 61,441 cases of syphilis in pregnant women (detection rate of 21.6/100,000 live births); 22,065 cases of congenital syphilis (incidence rate of 7.7/100,000 live births); and 186 deaths from congenital syphilis (mortality rate of 6.5/100,000 live births) were reported in the Notifiable Diseases Information System (SINAN).[7]

The underreporting of cases can mean these numbers are even higher and is part of the major problems in the fight against syphilis. In the care of patients with a positive test for syphilis, quality time is needed to clear the patient's doubts, make referrals, record the evolution and, finally, make the notification.[5]

Note that, although syphilis is amenable to prevention, diagnosis, and treatment in PHC, the disease still affects pregnant women and neonates. In this context, this study aimed to discuss the key points in the prevention and effective treatment of gestational syphilis in the context of the different levels of health care.

METHODS

This is a descriptive, retrospective, and cross-sectional study based on a survey in a public mother-child hospital in Porto Alegre, RS, Brazil, from January to June 2021. The hospital is a state reference in the area, receives referrals from PHC units and has 180 beds, it also treated 1,799 pregnant women in the obstetric center during the study period, according to records of the computerized system. The patients are referred by the primary care network of the municipality, as well those of municipalities in the interior of the state since it is a reference service in the area.

A survey of the notifications of syphilis in pregnant women and congenital syphilis was carried out with the SINAN. The variables date of diagnosis and notification, data from laboratory tests, treatment and prenatal care of the patients attended were consulted in the notifications of the Hospital Infection Control Service, in electronic medical records and in the e-SUS system. This survey seeks to bring complementary and relevant information to the services, since the different systems do not have an interface. Among the reported cases, one was selected since the patient had two records of hospital care at the Obstetric Center. Thus, the case was selected by the researchers to reflect on the role of different levels of health care in the prevention and treatment of syphilis during pregnancy.

This study is part of the matrix project entitled *"Ações de Farmácia Clínica no* Âmbito *da Saúde da Criança e da Mulher"* (Clinical Pharmacy Actions in the Scope of Child and Women's Health), which was approved by the Research Ethics Committee of the Hospital Materno Infantil Presidente Vargas (Opinion No. 4,716,657).

RESULTS

A total of 1,799 pregnant women were treated at the Obstetric Center of the study site, from January to June 2021, among which 17 cases of syphilis in pregnant women and 102 cases of congenital syphilis were reported. Among them, one case was selected as follows:

A 28-year-old patient, smoker, user of marijuana and cocaine for about eleven years, with no other comorbidities. She has had a steady partner for about five years and denies that he uses substances except alcohol. In her third pregnancy, her first daughter is 3 years old and lives with the patient's sister. She was admitted to the obstetric center on February 23, 2021, without information of gestational age, and informed that she did not undergo prenatal care. During the obstetric examination, a gestational age of 38 weeks and 2 days was verified, and a positive result for syphilis. The live baby was referred to the

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intensive care unit (ICU) for follow-up and necessary care.

Throughout the hospitalization, the patient reported recent psychiatric hospitalization and follow-up in the Psychosocial Care Center (CAPS), but without adherence to drug and behavioral treatment. In an interview with the Social Service, she showed interest in performing follow-up, affirming the birth of her child as a great motivator. Contradictorily, on the same day, the patient fled. The maternity hospital sent reports to the competent sectors and requested protective measures for the newborn (NB), who was discharged with institutional care and is still under outpatient health follow-up.

Records were found in the e-SUS as of January 14, 2020, confirming that the patient did not undergo prenatal care and, consequently, was not referred to the High-Risk Prenatal Service (PNAR) available at the study hospital, or another reference service.

During the review of the medical record data, a new admission of the same patient was found on January 13, 2022, taken in by the Mobile Emergency Care Service for evaluation in the same obstetric center due to the ruptured sac and twin pregnancy. The patient reported not having undergone prenatal care and provided the same information regarding social issues, she also indicated her last use of cocaine on January 12, 2021. Upon admission, blood typing tests and serology were performed, with a new test for reactive syphilis (laboratory test with VDRL result 1:8).

To start treatment for syphilis, the patient received a dose of benzylpenicillin 2,400,000 IU and was referred for hospitalization. The first twin was born in bed, a live birth, and the second was born in the delivery room, a live birth, both female, and were referred to the neonatal ICU for treatment of congenital syphilis and microcephaly investigation. Both were discharged with institutional care, with no record of outpatient follow-up at the service.

Followed-up by the psychiatry service, the patient was open to talking, but when approached about substance use, she became uncollaborative. In addition, the patient presented good health status and was discharged from the hospital with referral to primary care for follow-up of syphilis treatment, with prescription of benzylpenicillin, initiation of medroxyprogesterone, as a contraceptive method, and family planning guidance, with indication for placement of contraceptive implant, she was also referred to the CAPS for follow-up.

According to the evolution in the e-SUS system, it was found that the patient belongs to the territory of another health unit, so she was instructed to seek her referral unit to continue the follow-up. There is no information about the follow-up.

The case presented illustrates the patient's itinerary in PHC and in specialized services, such as CAPS and PNAR, in addition to hospital care, demonstrating the availability of care and, at the same time, the fragmentation of services. Management of syphilis is ineffective, even if prevention and treatment at the PHC level are possible.

DISCUSSION

During the study period, 17 cases of syphilis in pregnant women and 102 cases of congenital syphilis were reported. Such discrepancy may have occurred due to previous notification of pregnant women in PHC, or due to underreporting in the hospital environment.

Syphilis is a notifiable disease for all countries that are members of the WHO, and each case need to be investigated. In Brazil, the compulsory notification of congenital syphilis throughout the national territory was established by Ordinance No. 542, of December 22, 1986; syphilis in pregnant women, by Ordinance No. 33, of July 14, 2005; and that of acquired syphilis, by Ordinance No. 2,472, of August 31, 2010. The current ordinance that defines the Brazilian National List of Mandatory Notification of Diseases, Injuries, and Public Health Events in public and private health services throughout the national territory is Ordinance No. 264, of February 17, 2020.[7]

The underreporting of syphilis cases makes it difficult to combat the disease. The gap in the transfer of information can impair the integrality of care and longitudinal care from the point of primary and/or secondary care.

The case presented here represents several aspects involved in health care in cases of gestational and congenital syphilis. Extreme social vulnerability and the use of psychoactive substances stand out as factors that led to the lack of adequate prenatal care, as described by different professionals in the records analyzed. The fragmentation of the care process and the difficulty of access to continuity of care is also noticeable. After hospital discharge, the patient was referred to PHC for syphilis treatment follow-up, family planning guidance, and mental health follow-up, but no follow-up demonstrated the effective performance of subsequent care. However, establishing an integrated care network, with knowledge of the patients' itinerary and monitoring of the weak points of follow-up in the local reality is essential, considering that access and quality of care available to pregnant women, especially in PHC, are fundamental for the prevention, diagnosis, and treatment of gestational syphilis.[8-10]

We also found the absence of data recorded in the medical records of the hospital and of detailed description of the care provided in the PHC and recorded in the e-SUS, which does not make it clear whether the case of syphilis was notified. The lack of integration of computerized systems hinders the adequate follow-up of patients who access different levels of health care. In cases such as the one presented, professionals base their decisions on information provided by the patient, susceptible to memory bias, difficulties in expressing and understanding previous care, or even intentional omission of information.

The survey of notifications at the study site showed that, in 17 cases, the notification was made at the time of hospital care, that is, the diagnosis occurred in prepartum care, despite the fact that syphilis is a condition that can be prevented and treated in PHC. In this context, the Ministry of Health has adopted strategies to improve

syphilis surveillance in pregnant women, including the use of rapid tests, which can optimize the routine in health services and ensure testing for syphilis in prenatal programs, according to the guidelines applied in Brazil, especially in areas of difficult access to an effective laboratory network. The decentralization of rapid testing in PHC and maternity services can provide prompt diagnosis and appropriate treatment, especially when it comes to pregnant women and populations with greater vulnerability to syphilis.[10,11]

After treatment, the control of cure of syphilis in pregnant women should occur monthly by monitoring the fall of the titers of the venereal disease research laboratory (VDRL) test, which did not happen in the presented case. Non-treponemal tests are useful to investigate active syphilis and monitor treatment, by comparing the titer of the diagnosis with the titers of the post-treatment.[11]

Prenatal care is indispensable for the possible diagnosis of various diseases in pregnant women that can affect the baby. The prenatal care process indicators were determined considering the first visit up to the 12th week of gestation, minimum of six consultations, laboratory tests (blood count, serology for syphilis-VDRL, anti-HIV testing, and urinalysis), clinical-obstetric evaluation (blood pressure measurement, weight measurement, fundal height measurement, evaluation of fetal heart rate, and clinical breast exam), counseling related to the use of tobacco, alcohol and hair dye, absence from consultations, healthy eating and guidance regarding signs of labor and obstetric risk, instructions on breastfeeding and on the reference maternity for childbirth care. Referrals to specialized services when necessary are also possible.[12]

In Brazil, prenatal care is offered by the Unified Health System (SUS); however, adherence is still low, and the factors are the most diverse. A survey of the quality of prenatal care in Brazil, under the National Program for the Improvement of Access and Quality of Primary Care (PMAQ-AB), showed that only 15% of the 6,125 pregnant women interviewed received adequate prenatal care, considering all the actions recommended by the Ministry of Health. The proportion of complete care in pregnant women was significantly higher among those with older age, higher income, in the Southeast region, and in municipalities with more than 300,000 inhabitants and whose Human Development Index (HDI) is in the top quartile.[12] The findings of the second cycle of the PMAQ-AB indicate the need to expand the offer of diagnosis and treatment of syphilis to avoid and reduce vertical transmission.[13]

Other Brazilian studies point to flaws in prenatal care and inadequate treatment of syphilis cases.[14,15] An epidemiological study with 268 pregnant women with syphilis in a hospital in Minas Gerais, between 2007 and 2016, showed a diagnosis of congenital infection in 74.2% of the cases, which was significantly associated with inadequate prenatal care, absent/incomplete treatment, prematurity, and low birth weight.[16] Thus, new strategies are needed to reduce the transmission of syphilis during pregnancy, such as sexual education that contemplates the contagion and transmission of the disease, access to treatment, monitoring the treatment of the pregnant woman and her partner, presenting of the consequences of congenital syphilis and its relationship with inadequate treatment.[14]

Social and individual inequalities persist that can be the object of actions to qualify the work processes of the teams,[15] since there is a failure in the communication and articulation between health services at the three levels of care, disqualifying the concept of integrality of maternal and child care.[16] In this context, longitudinal care allows adequate follow-up, from pregnancy to the puerperium, in addition to providing subsidies for early identification of complications and increased satisfaction and adherence to postpartum consultations.[17]

Pregnant women exposed to social vulnerability and who are users of drugs and other substances make up the profile that most needs health support and, generally, are the ones who least adhere to prenatal care, as shown in the case reported in this study. Detecting pregnant women at higher risk of drug use during prenatal care may allow early intervention, reduction of health risk behaviors, and improvement of the quality of maternal and child care.[18]

The reported case puts us in front of several aspects of social vulnerability, which can impact access to health services. In this case, we can highlight the lack of assistance in the treatment of mental health and the lack of active search strategies for prenatal care in the Family Health Strategy (FHS), for guidance on family planning, and for referral to a specialized care service in high-risk pregnancies. In addition, the bond between patients and professionals brings more comfort and confidence, improving the care process. Care models that use indicators based on an absolute number of visits may hinder the patient's bond with professionals and directly reflect on the decrease in the quality of care.

For adequate treatment, part of the cases requires frequent consultations with health services, which may represent costs with travel and absences due to work activities. Thus, in addition to geographical accessibility, considering aspects related to functional accessibility, such as the functioning hours of the Basic Health Unit (BHU) and the organization of the flow of care for users so that they feel welcomed is necessary.[13]

Many pregnant women in situations of extreme vulnerability may have difficulty, or feel intimidated, to report to their partner the condition of an STI. Such aspects may be important elements for the low adherence and the large number of therapeutic failures regarding syphilis.[4] In the presented case, although the patient reported that she had had a steady partner for five years, no records were found regarding his testing or treatment.[6]

The pharmaceutical assistance of each municipality is responsible for the programming, acquisition, and distribution of the drug used, which is provided by the Ministry of Health via programs to combat and control STIs. The pharmacist must be integrated with the epidemiological data of the disease in his territory to avoid gaps in supply. The pharmacist is part of the multidisci-

plinary PHC team and can act both in the logistical part of the pharmaceutical care cycle and in the clinical part, performing orientation actions in drug dispensing, health education in groups of pregnant women, and testing actions. Thus, the pharmacist should be inserted in a multidisciplinary team, to promote comprehensive care for mothers and babies.

Pharmaceutical care is the practice model that guides the provision of different pharmaceutical services directly aimed at the patient, the family, and the community, aiming at prevention and resolution of pharmacotherapy problems, rational and optimal use of medicines, and promotion, protection and recovery of health, as well as the prevention of diseases and other health problems.[19]

This study had some limitations, such as the lack of data in the records or the low quality of the data. For these reasons, data collection in different data sources (notification forms and medical records) was included to minimize these problems. On the other hand, this case illustrates the complexity of attending to a condition considered sensitive to PHC.

Moreover, this study demonstrates the fundamental role of health care networks in the prevention and treatment of syphilis during pregnancy. The control of mother-to-child transmission of syphilis is a condition sensitive to PHC, and improving access to and quality of prenatal care, promoting syphilis testing, and ensuring adequate and immediate treatment of the pregnant woman and her partner is necessary, in addition to training health professionals to perform screening and early identification of cases.[20]

In addition, involving the different levels of health care in joint actions with a multidisciplinary character, aiming at interrupting the chain of transmission and preventing possible complications of congenital syphilis, is essential.

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AUTHORS' CONTRIBUTIONS

Janaína Vieira Belusso, Gabriela Bottan, and **Karin Hepp Schwambach** contributed to the conception, design, analysis, and writing of the article; **Janaína Vieira Belusso, Matheus William Becker, Gabriela Bottan,** and **Karin Hepp Schwambach** contributed to the review and final approval of the article. 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.

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

Revista de Epidemiologia e Controle de Infecção

Hospital Santa Cruz

ORIGINAL ARTICLE

Epidemiological survey on the benefit of neuraminidase inhibitors on severe acute respiratory syndrome due to COVID-19

Levantamento epidemiológico do benefício de inibidores de neuraminidase na síndrome respiratória aguda grave por COVID-19

Encuesta epidemiológica del beneficio de inhibidores de neuraminidase en síndrome respiratorio agudo severo por COVID-19

https://doi.org/10.17058/reci.v13i1.17973

Received: *03/11/2022*
Accepted: *23/12/2022*
Available online: *06/03/2023*

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ABSTRACT

Background and objectives: The COVID-19 pandemic and its consequent severe acute respiratory syndrome (SARS) have taken the lives of millions since 2020. The use of neuraminidase inhibitors is a promising alternative in treating this disease, with several studies on off-label use being conducted since the beginning of the pandemic, but none of them have a large sample size and analyze multiple risk factors. The purpose of this article is to identify possible associations between various factors and risk of hospitalization, need for ventilation and death, as well as the influence of the prescription of Zanamivir and Oseltamivir on these same indicators. **Methods**: In this transversal study, approximately 900,000 medical records from all regions of Brazil were collected from the Ministry of Health database, and after that, proper statistical analysis of the variables was performed. **Results:** Hospitalization was associated with gender, ethnicity, education, local urbanization, State, and its percentage of elderly, as well as the climate. The prescription of Zanamivir and Oseltamivir was associated with higher incidence of symptoms, lower hospitalization and death rate, and lower need for invasive and non-invasive ventilation. Medical records from146,160 patients were excluded due to SARS not caused by COVID-19. **Conclusion:** From this data, it is possible to draw a risk profile for hospitalization by SARS and consider the use of Zanamivir and Oseltamivir as a treatment for these patients.

Keywords: *SARS. Zanamivir. Oseltamivir. Covid-19.*

RESUMO

Justificativa e objetivos: A pandemia de COVID-19 e sua consequente síndrome respiratória aguda grave (SRAG) levaram milhões de pessoas a óbito desde 2020. O uso de inibidores da neuraminidase é uma alternativa promissora no tratamento dessa doença, com vários estudos sobre o uso *off-label* sendo conduzidos desde o início da pandemia, mas nenhum que tenha um grande tamanho amostral e que analise vários fatores de risco. O objetivo

Please cite this article as: *Flores, T. G., Antunes Gonçalves, C. F., Barbisan, F., Manica da Cruz, I. B., Agostini Lampert, M., Cardoso de Afonso Bonotto, N., & Niero Volpato, I. (2023). Levantamento epidemiológico do benefício de inibidores de neuraminidase na síndrome respiratória aguda grave por COVID-19. Revista De Epidemiologia E Controle De Infecção, 13(1). https://doi.org/10.17058/reci.v13i1.17973*

deste artigo é identificar possíveis associações entre diversos fatores e risco de hospitalização, necessidade de ventilação e óbito, assim como a influência da prescrição de Zanamivir e Oseltamivir nos mesmos indicadores. **Métodos:** Neste estudo transversal, foi feito o levantamento de aproximadamente 900 mil prontuários de todas as regiões do Brasil, provenientes de dados do Ministério da Saúde, e em seguida foi realizado o tratamento estatístico adequado das variáveis. **Resultados:** A hospitalização foi associada a sexo, etnia, escolaridade, urbanização do local, Estado e porcentagem de idosos do mesmo, assim como o clima. Já a prescrição de Zanamivir e Oseltamivir foi associada a maior incidência de sintomas, menor taxa de hospitalização e óbito e menor necessidade de ventilação invasiva e não-invasiva. Foram excluídos 146.160 prontuários devido a SRAG não ocasionada pela COVID-19. **Conclusão:** Com esses dados, é possível traçar um perfil de risco para hospitalização por SRAG e considerar o uso de Zanamivir e Oseltamivir como tratamento para esses pacientes.

Descritores: *SRAG. Zanamivir. Oseltamivir. Covid-19.*

RESUMEN

Justificación y objetivos: la pandemia Covid-19 y su consiguiente síndrome respiratorio agudo severo (SRAS) han muerto millones de personas desde 2020. El uso de inhibidores de la neuraminidasa es una alternativa prometedora en el tratamiento de esta enfermedad, con varios estudios sobre el uso *off-label* que se realiza desde el principio de la pandemia, pero ninguno que tenga un tamaño de muestra grande y analice múltiples factores de riesgo. El propósito de este artículo es identificar posibles asociaciones entre varios factores y el riesgo de hospitalización, necesidad de ventilación y muerte, así como la influencia de la prescripción de Zanamivir y Oseltamivir en los mismos indicadores. **Métodos:** En este estudio transversal, se encuestaron a los datos del Ministerio de Salud de aproximadamente 900,000 registros de todas las regiones de Brasil, después de que se realizó un tratamiento estadístico adecuado de las variables. **Resultados**: La hospitalización se asoció con género, etnia, educación, urbanización del sitio, Estado y porcentaje de ancianos, así como el clima. La prescripción de zanamivir y oseltamivir se asoció con la mayor incidencia de síntomas, menor hospitalización y tasa de mortalidad y menor necesidad de ventilación invasiva y no invasiva. Se excluyeron 146,160 registros médicos debido a SRAS no causado por Covid-19. **Conclusión:** con estos datos, es posible dibujar un perfil de riesgo para la hospitalización por SRAS y considerar el uso de zanamivir y oseltamivir como tratamiento para estos pacientes.

Palabras clave: *SRAS. Zanamivir. Oseltamivir. Covid-19.*

INTRODUCTION

By mid-2016, the *Coronavirus* family of viruses had caused two pandemics that, despite the higher case fatality rate, did not present such a high transmissibility.[1] In 2019, a new viral pathology originating in Wuhan, China, which is caused by a new virus of the *Coronavirus* family, SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2), COVID-19, has caused more than 6 million deaths worldwide, with excess mortality — more than the expected deaths from all causes — estimated at 18 million.[2,3]

Its most severe symptom, the severe acute respiratory syndrome (SARS), is defined as bilateral pulmonary infiltrates and hypoxemia without evidence of cardiogenic pulmonary edema, commonly leading to death. SARS consists of inflammation-mediated pulmonary changes, such as increased permeability of the alveolar-capillary membrane, pulmonary edema with consequent reduction in pulmonary compliance, and changes in the ventilation/perfusion ratio.[4-8]

The clinical management of SARS consists of several pharmacological and non-pharmacological alternatives with the objective of containing viral proliferation and its consequent inflammatory response.[9] One of the alternatives are anti-influenza drugs, which act by inhibiting the viral enzyme neuraminidase, such as zanamivir and oseltamivir.

In this sense, it is observed that many patients were submitted to the use of neuraminidase inhibitors because these were already prescribed for the treatment of common influenza, since it is also viral-caused.[10] *In vitro* and *in vivo* studies suggest that the antiviral effect of these drugs is not directly on the virus, but rather by modulating the immune system, especially neutrophils, to fight the viral infection.[11,12] Because this class of drugs inhibits the active site of neuraminidase, which is similar to that of the S1 spike protein of SARS-CoV-2, it possibly offers similar pharmacological benefits. However, the impact of the use of these drugs on SARS mortality and its relationship with the etiologic agent needs more clinical evidence.

METHODS

In this observational and retrospective study, data was gathered from secondary sources from the Ministry of Health. The variables analyzed were: hospitalizations for SARS regardless of cause, use of neuraminidase inhibitors, age, sex, length of stay, need for intubation, hospitalization in intensive care unit and mortality.[13]

The total study population was 1,048,575 individuals who entered Brazil's public health system due to COVID-19 symptoms. This system collected medical records from all parts of the country, removed the identifi-

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cation of patients and made the compilation of data publicly accessible in a *Microsoft Excel* spreadsheet. Because the records were filled during the peak of COVID-19, some data was considered "ignored" in the database, thus being excluded from the sample. In addition to the ignored data, individuals with SARS that was not caused by COVID-19 or whose tests were inconclusive were also excluded, totaling 146,160 exclusions.

Statistical tests for association were used (χ^2 univariate analysis or Fisher's exact test), the correlation was performed by Spearman's correlation coefficient with Bonferroni correction to analyze the association of deaths with the use of neuraminidase inhibitors. The *Statistical Package for the Social Sciences* - SPSS (version 21) software was used for all statistical analyses. The data reported in this article is publicly available without personal identifiers.

RESULTS

In the period analyzed, it was identified that 1,048,575 individuals entered the database of the Ministry of Health due to SARS symptoms; of these, 146,160 were listed as ignored and were excluded from the analyses. The classification of SARS is shown in Table 1.

It was observed that 82.9% (n=747,925) of SARS cases were due to SARS-CoV-2, the etiologic agent of COVID-19, and that the other causes added together were responsible for the remaining 16.9% (n=154,490) of hospitalizations. The profile of hospitalizations by SARS classification is shown in table 2.

When analyzing table 2, it was observed that male sex was predominant in all types of SARS, the same occurring with the ethnicity that was predominantly white. The occurrence of SARS stratified by schooling was variable, where in SARS due to influenza (26.5%), in unknown etiological agent (27.1%) and not specific (25.7%), individuals with elementary education between 1st and 5th grade were predominant, while in SARS by other etiological agents there was a higher occurrence in individuals where schooling is not applied, such as immigrants or indigenous people, and in SARS due to COVID-19, the predominant level of schooling was high school (33.1%). The predominant place of residence in all types of SARS was urban.

The State that had the most SARS cases was São Paulo (21.1 %), followed by Minas Gerais (11.7%), Rio de Janeiro (7.4%) and Paraná (7.3%). The distribution of cases by region was as follows: Southeast (48.8%), Northeast (20.6%), South (17.7%), Midwest (9%) and North (6.5%).

In the population analyzed, 4.3% (n=29,845) of the individuals were prescribed neuraminidase inhibitors, whose prescription profile is shown in table 3.

Table 1. Classification of SARS cases (Brazil, 2021, n=902,415).

Etiological cause	N	%
Influenza	740	0.1
Unknown Etiological agent	1,715	0.2
Other respiratory viruses	5,461	0.6
Unspecified	146,574	16.2
COVID-19	747,925	82.9
Total	902,415	100

Table 2. SRAG profile (Brazil, 2021, n=902,415).

Characteristic	Etiological agent									
	Influenza		Other respiratory viruses		Unknown etiologic agent		Unspecified		COVID-19	
	n	%	n	%	n	%	n	%	n	%
Sex										
Female	328	44.3	2,465	45,1	789	46.0	70,459	48.1	332,807	44.5
Male	412	55.7	2,995	54,8	926	54.0	76,065	51.9	415,014	55.5
Ethnic group										
White	264	40.2	2,156	51,0	843	53.2	55,738	46.1	333,985	53.8
Black	28	4.3	190	4,5	107	6.7	7,520	6.2	30,357	4.9
Yellow	9	1.4	12	0,3	22	1.4	1,243	1.0	6,719	1.1
Brown	355	54.1	1,855	43,9	608	38.3	56,046	46.4	248,307	40.0
Indigenous	0	0.0	17	0,4	6	0.4	323	0.3	1,002	0.2
Schooling										
Illiterate	14	6.1	524	15.6	121	13.5	6,908	12.8	15,302	5.7
Elementary school	61	26.5	140	4.2	243	27.1	13,845	25.7	70,098	26.1
Middle school	33	14.3	58	1.7	230	25.7	7,869	14.6	50,572	18.9
High school	57	24.8	55	1.6	145	16.2	9,716	18.0	88,827	33.1
College	20	8.7	24	0.7	57	6.4	3,139	5.8	40,420	15.1
Not applicable	45	19.6	2,553	76.1	100	11.2	12,460	23.1	3,056	1.1
Zone										
Urban	585	92.9	4,479	94.1	1,398	91.2	12,2138	93.7	620,649	94.4
Rural	44	7.0	110	2.3	131	8.5	7,253	5.6	34,266	5.2
Suburban	1	0.2	172	3.6	4	0.3	942	0.7	2,216	0.3

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Table 3. Profile of the use of neuraminidase inhibitors (Brazil, 2021, n=902,415).

Characteristic	Prescription of neuraminidase inhibitors			
	YES		NO	
	n	%	n	%
Sex				
Female	13,553	45.4%	300,561	45.1%
Male	16,288	54.6%	366,248	54.9%
Ethnic group				
White	13,681	52.2%	307,012	53.6%
Black	1,388	5.3%	29,057	5.1%
Yellow	264	1.0%	5,839	1.0%
Brown	10,803	41.2%	229,914	40.1%
Indigenous	57	0.2%	947	0.2%
Schooling				
Illiterate	1,069	7.4%	19,680	7.1%
Elementary school	3,583	24.8%	72,566	26.0%
Middle school	2,314	16.0%	50,525	18.1%
High school	3,853	26.7%	84,643	30.3%
College	1,575	10.9%	35,387	12.7%
Not applicable	2,032	14.1%	16,288	5.8%
Zone				
Urban	25,173	92.5%	574,465	94.1%
Rural	1,875	6.9%	33,502	5.5%
Suburban	173	0.6%	2,635	0.4%

Table 4. Comparison of symptoms versus antiviral use (Brazil, 2021, n=902,415).

	Notification form variable ANTIVIRAL USE					
		YES		NO		
		n	%	n	%	*p-value*
Fever	Yes	17,847	68.0%	365,576	62.7%	
	No	8,393	32.0%	217,026	37.3%	
Cough	Yes	22,473	83.2%	456,561	75.9%	
	No	4,548	16.8%	144,645	24.1%	
Sore throat	Yes	6,046	27.3%	115,251	22.6%	
	No	16,132	72.7%	395,714	77.4%	
Dyspnea	Yes	22,348	82.5%	482,746	79.3%	
	No	4,754	17.5%	126,109	20.7%	
Respiratory	Yes	19,685	76.2%	397,027	69.1%	
distress	No	6,140	23.8%	177,562	30.9%	
Saturation	Yes	20,570	78.5%	456,771	76.7%	
	No	5,626	21.5%	139,101	23.3%	
Diarrhea	Yes	4,653	21.2%	91,985	18.1%	<0.001
	No	17,328	78.8%	416,184	81.9%	
Abdominal pain	Yes	2,159	10.2%	45,253	9.2%	
	No	18,905	89.8%	445,781	90.8%	
Fatigue	Yes	9,335	41.6%	187,251	36.4%	
	No	13,124	58.4%	32,7624	63.6%	
Loss of smell	Yes	3,392	16.0%	63,732	12.9%	
	No	17,765	84.0%	429,877	87.1%	
Loss of taste	Yes	3,518	16.7%	64,880	13.2%	
	No	17,598	83.3%	428,137	86.8%	
Vomiting	Yes	3,130	14.4%	61,783	12.3%	
	No	18,544	85.6%	439,330	87.7%	

The mean age of individuals who used neuraminidase inhibitors was 50.08 years (± 24.52) and of those who did not use was 54.31 years (±20.55).

The prescription of neuraminidase inhibitors was associated with ethnicity (p<0.001), schooling (p<0.001) and zone of residence (p<0.001), with no association with gender.

The presentation of symptoms in individuals who were prescribed neuraminidase inhibitors was significantly different when compared to those who did not have the prescription, as can be analyzed in table 4.

Individuals who were prescribed neuraminidase inhibitors were more likely to have fever (1.250; CI: 1.229 to 1.296), cough (1.539; CI 1.491 to 1.588), sore throat (1.273;CI: 1236 to 1.310), dyspnea (1.218 CI: 1.181 to 1.256), respiratory distress (1.413; CI: 1.374 to 1.454), changes in O_2 saturation (1.109: CI;1.077 to 1.141), diarrhea (1.205;CI: 1.167 to 1.243), abdominal pain (1.119:CI; 1.072 to 1.169), fatigue (1.233;CI: 1.201 to 1.265), loss of smell (1.273; CI: 1.229 to 1.320), loss of taste (1.303; CI: 1.258 to 1.350) and vomiting (1.191: CI; 1.191 to 1.147).

The fact that the symptoms were more prevalent did not translate into a higher rate of hospitalization in the intensive care unit (ICU) or use of ventilatory support, with 30.2% (n=7,783) of the individuals who used neuraminidase inhibitors being admitted to the ICU against 30.8% (n=189,485) of those who did not. In fact, there is an inverse association of the use of neuraminidase inhibitors and ICU admission, with a higher risk for individuals who were not prescribed (1.001; CI 1.000 to 1.002, *p=0.023*).

Regarding the use of ventilation, individuals who used neuraminidase inhibitors had a higher percentage of noninvasive ventilation use (63.7%), followed by no use of ventilatory support (18.4%) and only 17.9% (n=4,650) used invasive ventilation. Those who did not use neuraminidase inhibitors had similar rates, with 63.4% (n=378,369) using noninvasive ventilation, 20.0% (n=123,179) not using ventilatory support and 18.7% (115,071) using invasive ventilation. There was an inverse association between the use of neuraminidase inhibitors and ventilatory support (p<0.001). Non-prescription of neuraminidase inhibitors increased the chance of using invasive mechanical ventilation by 1.159 (CI: 1.056 to 1.273).

Death occurred in 34.3% (n=174,028) of the cases. Of these, 3.9% (n=6,701) had been prescribed neuraminidase inhibitors and 96.1% (n=167,327) had no prescription. The use of neuraminidase inhibitors was associated with a higher chance of cure (p<0.001), increasing it by 1.055 times (CI: 1.045 to 1.065).

There was no difference between the classes of neuraminidase inhibitors (p=0.076).

In predicting cure, the antiviral drug Oseltamivir had prediction, with significance of p=0.027 and Exp(β) of 1.095 (CI: 1.010 to 1.187).

DISCUSSION

The use of neuraminidase inhibitors was associated with a higher incidence of symptoms, probably as a result of the greater severity of the patients' clinical case with prescription indication. Some studies indicate that although there

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is a positive association between the use of neuraminidase inhibitors and increased symptoms, the risk of admission to the ICU was higher for patients who did not use these drugs.[11] As large-scale ICU admission overwhelms the health system, the adoption of neuraminidase inhibitors for symptomatic patients becomes a very relevant public health tool.

In cases of hospitalization, the need for invasive mechanical ventilation was lower in patients who used neuraminidase inhibitors. The data reinforces the suggestion that these drugs be used in large scale in the healthcare system. In addition, the death rate was lower in patients who had a prescription. Thus, the results suggest the indication of neuraminidase inhibitors prescription as a treatment for SARS complications, increasing the chance of cure. Other studies suggest a positive correlation between the use of neuraminidase inhibitors before treatment and shorter hospital stays, which also avoids the situation of lack of ICU beds.[14]

With the arrival of COVID-19 in Brazil, there was an increase in cases of hospitalization for SARS, a result observed in our etiological analysis. When analyzing the causes of hospitalization for SARS, the main cause identified was the SARS-CoV-2 virus.[2,15]

When analyzing the epidemiological characteristics, such as gender, we observed that male sex had a predominance in SARS cases regardless of the etiological agent. This finding converges with those found in other studies already carried out, which indicate greater susceptibility to infections and higher mortality associated with this disease in males.[16,17]

Another finding is the predominance of white ethnicity in SARS-CoV-2 SARS cases. This phenomenon is possibly a result of greater access to laboratory tests by this ethnic group, with underreporting occurring in the others as a result of non-testing, and the situation as a whole is a consequence of social inequalities.[18,19]

The data also showed an association between schooling and hospitalization for SARS. It is noticed that cases of SARS by SARS-CoV-2 are more frequent in people with complete high school education, while cases of contagion by influenza, unknown and non-specific etiological agent are more frequent in the population niche of elementary education between 1st and 5th grade. This data suggests that SARS-CoV-2 has a tendency to infect individuals with a higher level of education compared to other etiologic agents, but the possibility of underreporting makes it impossible to be sure of this conclusion. As education level is associated with socioeconomic status, and SARS-CoV-2 possibly had its initial spread by means of tourist transport, such as planes and ships, these restricted to individuals with higher purchasing power, the association between cases and level of education is possibly another reflection of social inequalities.[20]

In addition, there was a relationship with zone of residence. The results indicate a higher incidence of SARS of all etiological agents in urban areas. This data can be justified by the fact that these regions have a higher rate of contagion due to the difficulty of maintaining social distancing and the fact that the majority of the Brazilian population lives in urban areas, as indicated by the latest data from IBGE (The Brazilian Statistics Bureau).[21]

It is noticed that the most populous states such as São Paulo, Minas Gerais and Rio de Janeiro reported higher numbers of SARS cases, and this results from several factors, such as the proportional relationship between population density and contagion, as evidenced in other studies, and also the late adoption of social distancing by some States, notably Rio de Janeiro.[15,22]

Finalizing the relationships between SARS and demographics, a relationship was observed between hospitalizations and percentage of elderly people in the States. The data shows that in the southern States, which have a higher proportion of elderly population, SARS rates are higher, which confirms previous knowledge of other studies that indicate higher rates of complications of the disease in the elderly.[21,23]

Another factor that explains the relationship between the proportion of elderly and hospitalization for SARS is the climate. The southern region of the country has a subtropical climate, which increases the rate of contagion.

Regarding the prescription of neuraminidase inhibitors, white patients had proportionally more prescription of neuraminidase inhibitors in relation to other ethnicities, possibly because the latter had on average better economic condition and access to healthcare, as well as higher rates of testing and drug prescription.[18]

The prescription of neuraminidase inhibitors was associated with lower schooling. This data may be due to the prophylactic measures instituted by the Ministry of Health, which mostly covers public hospitals, where the profile of the average patient is less educated compared to private hospitals, which have a larger structure and more effective medications. On the other hand, there are studies that demonstrate lower morbidity and mortality in populations with higher educational level in Brazil and the USA.[24]

The limitations of this study are related to data collection since there is no system of digital medical records in the Brazilian public health system and this fact limits the scope of the data. We can also affirm that there is a limitation associated with filling out the forms, a fact that culminated in the exclusion of medical records.

With the data presented, a patient profile more conducive to hospitalization, need for invasive or non-invasive ventilation and death from SARS can be visualized. This profile can be used as a basis for the preparation of screening protocols in health units, as well as updating treatment guidelines for patients with SARS in their various presentations.[25] An association can also be observed between prescription of Zanamivir and Oseltamivir and lower rates of hospitalization and death, as well as less need for invasive and non-invasive ventilation, suggesting the use of these neuraminidase inhibitors as a treatment for patients at risk as well as a public health tool to reduce the rate of bed occupancy in the healthcare system.

ACKNOWLEDGEMENTS

The present study was carried out with the support of Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES).

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AUTHORS' CONTRIBUTION

Carlos Fernando Antunes Gonçalves and **Isis Niero Volpato** contributed to the design, analysis and writing of the article;

Thamara Graziela Flores contributed to the conception, planning, design, writing, review and final approval of the article;

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

Revista de Epidemiologia e Controle de Infecção

Hospital Santa Cruz

ORIGINAL ARTICLE

Accuracy of mortality indicators due sepsis-associated deaths in the Federal District

Acurácia dos indicadores de mortalidade devido a sepse dos óbitos ocorridos no Distrito Federal

Precisión de los indicadores de mortalidad por sepsis de las defunciones ocurridas en el Distrito Federal

https://doi.org/10.17058/reci.v13i1.17621

Received: *10/05/2022*
Accepted: *16/07/2022*
Available online: *06/03/2023*

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ABSTRACT

Background: Sepsis currently represents a challenge for health systems, this fact may be related to the spread of bacterial resistance, the increase in the population of elderly, immunosuppressed individuals, and the improvement of emergency care, favoring the survival of critically ill patients. This article aimed to evaluate the accuracy of mortality indicators due to sepsis in 2018. **Method:** Validation study of death certificates that occurred in the Federal District in 2018. Declarations whose basic causes of death identified were classified as garbage codes were identified, which were investigated by a multidisciplinary team, capable of reclassifying them with codes that allow for the improvement of health data. In order to assess accuracy, sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratios of death certificates from sepsis were calculated, with 95% confidence intervals. **Results:** A total of 6.244 statements were evaluated, of which 233 (3.74%) presented sepsis as the underlying cause before being investigated and only 35 (0.56%) maintained it after the investigation. The filling of statements with sepsis as the underlying cause by physicians showed a sensitivity of 0.9% (95%CI: 0.6 to 1.3) and a specificity of 92.0% (95%CI: 90.9 to 93.1). **Conclusion:** The low accuracy of the declarations demonstrates the non-reliability of the underlying cause of death from sepsis, especially the completion of death certificates that occurred in the Federal District in 2018.

Keywords: Sepsis. Data Accuracy. Cause of Death. Death Certificates.

RESUMO

Justificativa: A sepse, atualmente, representa um desafio para os sistemas de saúde, tal fato pode estar relacionado com a disseminação da resistência bacteriana, o aumento da população de idosos, os indivíduos imunossuprimidos, e a melhoria do atendimento de emergência, favorecendo a sobrevivência de pacientes críticos. Este artigo

Please cite this article as: *Alves Ramires , F. ., Sousa Cruz e Silva , C. ., Costa Abreu , L. C. ., de Queiróz Pereira, A. L. . ., Ramos de Moraes Rego , E. ., Soares Barbosa de Carvalho , D., Silva Souza , E. ., Oliveira Lyrio, A., dos Santos Conceição , S. ., Morais Godoy Figueiredo , A. C. ., & Estrela Tuy Batista, J. (2023). Acurácia dos indicadores de mortalidade devido a sepse dos óbitos ocorridos no Distrito Federal. Revista De Epidemiologia E Controle De Infecção, 13(1). https://doi.org/10.17058/reci.v13i1.17621*

teve por objetivo avaliar a acurácia dos indicadores de mortalidade devido à sepse em 2018. **Método:** Estudo de validação da causa básica dos óbitos ocorridos no Distrito Federal em 2018. Foram identificadas as declarações de óbito cujas causas básicas de morte apontadas foram classificadas como *garbage code sepse,* as quais foram investigadas por uma equipe multidisciplinar, capacitada para reclassificá-las com códigos que permitem o aprimoramento dos dados em saúde. A fim de avaliar a acurácia, foram calculados os valores de sensibilidade, especificidade, valores preditivos positivo e negativo, razões de verossimilhança positiva e negativa das declarações dos óbitos por sepse, com intervalos de confiança de 95%. **Resultados:** Um total de 6.244 declarações foram avaliadas, das quais 233 (3,74%) apresentavam a sepse como causa básica antes de serem investigadas e apenas 35 (0,56%) mantiveram-na após a investigação. O preenchimento das declarações com a sepse enquanto causa básica pelos médicos apresentou sensibilidade de 0,9% ($IC_{95\%}$: 0,6 a 1,3) e especificidade de 92,0% ($IC_{95\%}$: 90,9 a 93,1). **Conclusão:** A baixa acurácia das declarações demonstra a não fidedignidade da causa básica de óbito por sepse, sobretudo, do preenchimento das declarações dos óbitos ocorridos no Distrito Federal em 2018.

Descritores: Sepse. Confiabilidade dos Dados. Causas de Morte. Atestado de Óbito.

RESUMEN

Justificación: Sepsis representa en la actualidad un desafío para los sistemas de salud, este hecho puede estar relacionado con propagación de resistencias bacterianas, aumento de la población de ancianos, inmunodeprimidos, y mejora de la atención de urgencias, favoreciendo la supervivencia de los pacientes críticos. Este artículo tuvo como objetivo evaluar la precisión de los indicadores de mortalidad por sepsis en 2018. Método: Estudio de validación de causa básica de muertes ocurridas en Distrito Federal en 2018. Se identificaron actas de defunción cuyas causas básicas de muerte fueron clasificadas como sepsis código basura y fueron investigadas por un equipo multidisciplinario capacitado para reclasificarlas con códigos que permitan la mejora de datos de salud. Para evaluar la precisión, se calcularon sensibilidad, especificidad, valores predictivos positivo y negativo y razones de verosimilitud positiva y negativa de certificados de defunción por sepsis, con intervalos de confianza del 95%. **Resultados:** se evaluaron 6.244 declaraciones, de las cuales 233 (3,74%) tenían como causa básica la sepsis antes de ser investigadas y solo 35 (0,56%) mantuvieron después de investigación. Realización de declaraciones con sepsis como causa subyacente por parte de los médicos mostró sensibilidad del 0,9% (95%IC: 0,6 a 1,3) y especificidad del 92,0% (95%IC: 90,9 a 93,1). **Conclusión:** Baja precisión de las declaraciones demuestra la poca confiabilidad de la causa subyacente de muerte por sepsis, especialmente la finalización de los certificados de defunción ocurridos en Distrito Federal en 2018.

Palabras clave: Sepsis. Exactitud de los Datos. Causas de Muerte. Certificado de Defunción.

INTRODUCTION

Sepsis consists of potentially fatal organic dysfunction triggered by the dysregulation of the host's immune response to infections. Sepsis is diagnosed from the association between multiple organ failure and suspected or confirmed infectious processes.[1–3] Classically, the characteristic organic dysfunction of sepsis is diagnosed by scores of two or more points on the Sequential Organ Failure Assessment (SOFA) scale, which assesses the functioning of the central, cardiovascular, respiratory and renal nervous systems, in addition to liver and platelet function.[1] Sepsis and septic shock are associated with significant morbidity and mortality in individuals admitted to the intensive care unit (ICU) because they acquire hospital infections more frequently.[1,4]

Risk factors for sepsis are extremes of age, a sedentary lifestyle, immunosuppression, alcohol consumption, cancer, diabetes, and prolonged use of catheters or other conditions that compromise skin integrity. However, among patients with established infections, other risk factors for sepsis have been reported, such as comorbidities and genetic factors of the host and infectious agent.[1] ICU admission, previous hospitalizations, bacteremia, obesity and community-acquired pneumonia have also been described as potential risk factors for sepsis.[4]

Today, sepsis represents a growing challenge for health systems in countries around the world. With the advancement of health technologies, the longevity of the populations most vulnerable to sepsis, such as elderly and immunocompromised patients have increased, thus leading to a subsequent increased incidence of sepsis. It is estimated that 17 million cases of sepsis occur worldwide each year, but estimates are likely to underestimate the actual number of cases.[5]

It is believed that 600,000 of the annual cases of sepsis occur in Brazil, where the lethality rates of sepsis and septic shock exceeded 30% and 60%, respectively, in 2003.[5] In 2015 alone, 110,049 hospitalizations for sepsis were recorded in the country, of which only 925 occurred in the Federal District. However, the federative unit had the highest average length of hospital stay, at 20.11 days, and ranked eighth in the sepsis mortality rate, which corresponded to 50.38%.[6]

In addition to triggering significant morbidity and mortality, sepsis negatively impacts health systems in re-

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lation to bed occupancy and hospital costs. Estimates indicate that approximately 30% of Brazilian ICU vacancies are occupied by individuals with sepsis or septic shock. In addition, for each hospitalized patient, the average hospitalization cost is $10,595.00.[5]

Although sepsis has higher lethality rates in underdeveloped or developing countries5, the vast majority of scientific publications on the subject come from developed countries. Perceived disproportionality skews the available evidence regarding sepsis, which may compromise understanding of the subject in contexts of countries with limited resources.[1] Therefore, it is likely that the underestimation of the incidence of sepsis in underdeveloped countries compromises the direction of resources for the study and treatment of sepsis regionally.

Therefore, especially in countries with limited resources, such as Brazil, the expansion of epidemiological data on sepsis, along with the implementation of public policies aimed at the prevention and proper management of sepsis nationally, and determining the underlying cause of death would all help to improve healthcare for septic patients. Thus, this study, conducted in the Federal District, aimed to evaluate the accuracy of mortality indicators due to sepsis in 2018.

METHODS

Study design and context

A validation study was conducted in the Federal District, which has the smallest territory and one of the smallest populations among the federative units in Brazil. The estimated population of the Federal District in 2021 corresponded to 3,094,325 individuals.[7] At the same time, the federative unit has the highest population density and the highest income in the country[7], in addition to the second highest rate of life expectancy at birth, which was estimated to be 77.6 years in 2014.[8]

Data source, investigation steps and data collection procedures

Data collection for this research was carried out at the State Department of Health of the Federal District (SES-DF). This department manages mortality information systems, as well as diseases, injuries and compulsory notification events in the Federal District.[9] In Brazil, mortality data are regulated through the Mortality Information System (SIM), whose standard document corresponds to death certificates.[10]

The information was collected through a standardized form (elaborated by the authors) based on the screening and investigation of potentially eligible death certificates. During screening, the garbage codes used *in field* 40 of the document, referring to the causes of death related to sepsis, were identified. Medical records, examinations and reports issued by health institutions linked to death certificates were accessed by the exclusive SES-DF system and analyzed. The information collected is presented and described in the variables section.

Population and eligibility criteria

In this study, the population was composed of people who died in the Federal District in 2018, whose underlying causes of death indicated sepsis, represented in the International Classification of Diseases version 10 (ICD 10) by codes A40, A40.0, A40.1, A40.2, A40.3, A40.9, A41.0, A41.1, A41.2, A41.3, A41.4, A41.5 and A41.9; all death certificates of children under one year of age were excluded. Sepsis is considered a *garbage code*[11]. *Garbage codes* are basic causes of death that do not provide fundamental information about the triggering circumstance of death, so a valid underlying cause of death is not understood.

Variables

The main variable of this study is sepsis, as the underlying cause of death, which is recorded on the death certificate. In addition, other variables were used to characterize the population, which included age ranges (1 to 11 years, 12 to 18 years, 19 to 39 years, 40 to 59 years, and 60 years or more), sex (male and female), race or skin color (Asian, white, indigenous, African American and black), years of study (none, 1 to 3 years, 4 to 7 years, 8 to 12 years, 12 years or more), marital status (divorced/single/widowed and married/stable union), and place of death (hospital, other health facilities and other places).

Data analysis

After data collection, the underlying causes of death from sepsis were compared, recorded in the original statements and the causes defined after the investigation by the multidisciplinary team, which was considered the gold standard. Subsequently, the death certificates were divided into four groups: true-positive, false-positive, true-negative and false-negative.

In the true-positive group, the death certificates that remained with the same underlying cause after the investigation, were grouped. The false-positive group included death certificates that initially had the underlying cause of death from sepsis but were reclassified to others after being investigated. In the true-negative group, all declarations that did not present the cause of sepsis and remained with the original underlying cause of death after the investigation were grouped. In the false-negative group, all statements that had another underlying cause and were reclassified for sepsis after investigation were included.

Finally, sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio and negative likelihood ratio were estimated, with 95% confidence intervals. Data analysis was performed using the data analysis and *statistical software* (STATA) statistical package, version 16.

The research was conducted respecting the ethical standards required in Resolutions 466/2012, 510/2016 and 580/2018 of the Ministry of Health and was approved by the Research Ethics Committee (CEP) of the School of Health Sciences (ESCS), CAAE:15457719.0.0000.5553, under opinion number 4,482,501. The researchers involved claim no conflicts of interest related to the development of the study.

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RESULTS

At the end of the data analysis, 6,244 death certificates were evaluated. The population analyzed had a mean age of 62.78 years (standard deviation ± 22.35) and a median of 67 years, whose amplitude was 1 to 112 years. Most deaths occurred among patients aged 60 years or older, male, white skin color, divorced, single or widowed, and with 1 to 3 years of study. In most deaths, the place of occurrence was the hospital. Before being investigated, 233 declarations presented sepsis as the underlying cause, which corresponds to 3.74% of the population. After the investigation, only 35 statements had sepsis maintained as the underlying cause, which represents 0.56% of the results, as shown in Table 1. Therefore, the investigation of death certificates rectifies the underlying cause of 84.97% of the declarations.

Table 1. Number (N) and percentage (%) of the variables of characterization of deaths occurred in the Federal District in 2018 (N=6,244).

Variable	N	%
Sex*28		
Female	2.507	40,33
Male	3.709	59,67
Age (years)*38		
1 to 11	74	1.19
12 to 18	127	2.05
19 to 39	929	14.97
40 to 59	1.363	21.96
60 or more	3.713	59.83
Etnia/Raça/cor*79		
Asian	28	0.45
White	2.703	43.84
Indigenous	7	0.11
African American	2.895	46.96
Black	532	8.64
Marital status*285		
Divorced, single or widowed	3.972	66.67
Married or in stable union	1.987	33.33
Years of study*694		
None	896	16.14
1 to 3	1.463	26.36
4 to 7	1.290	23.24
8 to 11	1.266	22.82
12 or more	635	11.44
Place of death*28		
Hospital	5.116	82.30
Other health services	309	4.97
Other	791	12.73
Underlying cause of death prior to investigation		
Sepsis	233	3.74
Other underlying causes of death	6.011	96.26
Underlying cause of death after investigation		
Sepsis	35	0.56
Other underlying causes of death	6.209	99.44

**Number of information unavailable for each variable; N: sample; %: percentage.*

Table 2 shows that the sensitivity of the evaluated statements about sepsis was approximately 0.93% ($_{95\%}$ CI: 0.64 to 1.29). On the other hand, there was a high probability of an individual who did not develop sepsis obtaining a statement that did not present sepsis as the underlying cause, since the specificity found was 92.00% ($_{95\%\ CI}$: 90.90 to 93.10). The chance of a death certificate whose underlying cause was sepsis belonging to a septicemic individual was 15.00% ($_{95\%\ CI}$: 10.70 to 20.30), which consists of the positive predictive value of the evaluated statements. The probability of a declaration that the individual who did not develop sepsis as the underlying cause was 38.00% ($_{95\%}$ CI: 36.80 to 39.30), which represents the negative predictive value.

Additionally, according to Table 2, it was found that the chance of a death certificate indicating sepsis as the underlying cause is 0.12 times higher ($_{95\%\ CI}$: 0.08 to 0.16) for a septicemic person than for an individual with another underlying cause of death, which consists of the positive likelihood ratio of the evaluated statements. At the same time, the probability of a declaration not indicating sepsis as the underlying cause is 1.08 times higher for septicemic people than for individuals who have not developed sepsis, which corresponds to the negative likelihood ratio found.

Table 2. Validation measures and predictive characteristics of the death certificate for sepsis disease in 2018, Federal District (N= 6,244).

Parameter	Value	IC95%*
Sensitivity (%)	0.93	0.64 – 1.29
Specificity (%)	92.00	90.90 – 93.10
Positive predictive value (%)	15.00	10.70 – 20.30
Negative predictive value (%)	38.00	36.80 – 39.30
Positive likelihood ratio	0.11	0.08 – 0.16
Negative likelihood ratio	1.08	1.06 – 1.09

**Confidence interval at 95%; N: sample; CI: confidence interval.*

DISCUSSION

A total of 233 deaths that occurred in the Federal District in 2018 presented sepsis as the underlying cause in the death certificate before being investigated. Generally, the profile of the population studied consisted of males; White; divorced, single or widowed; 60 years or older; and low educational level. After the investigation, there were 35 statements left in which sepsis was the underlying cause of death. Thus, the investigation rectifies the underlying cause of 198 statements, which corresponded to 84.97% of the original 233. The death certificates evaluated showed low sensitivity and high specificity.

The profile of the participants in this study is similar to that described in the literature. In 2015, 53 patients were admitted to the ICU due to sepsis or septic shock at the University Hospital of Brasília (HUB). Most of the hospitalized patients were also male and older than 60 years, in addition to living in the Federal District or Goiás. Additionally, 90.60% of them had pathological antece-

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dents, including systemic arterial hypertension (SAH), diabetes mellitus (DM), maternal diseases and previous episodes of sepsis.[12]

Another investigation corroborated the findings of the survey, conducted in 2017, where 37,082 death certificates were investigated, which occurred in 17 municipalities in northern Brazil. During the screening of the documents, some of the underlying causes of death considered garbage codes were classified as priority, which included sepsis. After the investigation, 79.1% of the statements coded with garbage codes had the underlying cause rectified, and the number of deaths whose underlying cause was sepsis decreased by 24.9%.[13]

However, inadequate completion of the underlying cause in death certificates is not restricted to the aforementioned sites. Between 2007 and 2016, more than 4 million of the deaths in Brazil were reported with garbage codes as the underlying cause, which represented 34.0% of the total number of deaths. Thus, the investigation of these statements is essential for the improvement of health data.[13] According to DATASUS, in 2015 only, sepsis was responsible for 110,049 hospitalizations in the country, which incarcerated costs of R$400,387,078.76.6 In the event that health actions and public policies promote the effective improvement of the population's health conditions, in the tangent of sepsis to other diseases and diseases with high prevalence in Brazil, the quality of available health information is crucial.[13-15]

Moreover, this study presented limitations. Among them, the main one consists of inadequate completion of the death certificates analyzed, which was verified both in the face of unfilled fields and incorrect information. Of the 6,244 statements, 694 did not present the field referring to the years of study of the deceased completed, corresponding to 11.11% of the sample. It is likely that the misconceptions observed in the statements are due to medical ignorance about the importance of proper filling of all fields of the document, as well as the malpractice of the medical class in informing the chain of pathological events questioned in the field of cause of death.[13,16]

In addition, the second limitation of this study is the existence of outdated, incomplete or even blank medical records, referring to individuals who died, which was also reported in the study conducted at the hub in 2015.[6] Inadequate medical records may be related to the negligence of the responsible health professionals and the existence of multiple disintegrated electronic medical records systems, since care provided in certain health institutions may not be recorded in the medical records to which the researchers had access.

However, all death certificates whose underlying cause was a garbage code were investigated individually by a multidisciplinary and previously qualified team. Thus, in addition to rectifying the underlying epidemiological cause in the Mortality Information System by investigating the medical records and medical examination reports of individuals who died, the other fields filled out incorrectly or neglected were also corrected during the typing of the document whenever possible. The death review committees (CROs) of health institutions where the deaths occurred were also triggered in the face of outdated, incomplete or blank medical records to obtain the information necessary for the correct investigation of deaths. Moreover, this is the first study in the Federal District to evaluate the accuracy of death certificates that indicate sepsis as the underlying cause.

Death certificates that occurred in the Federal District in 2018 that indicated sepsis as the underlying cause of death, present low sensitivity and positive predictive value, which indicate the low reliability and low usefulness of mortality indicators due to sepsis for planning health actions and public policies. Nevertheless, the low accuracy of the statements demonstrates the lack of reliability of the diagnostic investigation of sepsis and, above all, of the completion of the declarations. The need for health institutions to implement programs aimed at improving the proper completion of death certificates and care for septicemic individuals is evident. Moreover, it is crucial that undergraduate medical courses and medical residency programs include the task of correctly completing death certificates as an educational objective.

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AUTHORS' CONTRIBUTIONS

Fernanda Alves Ramires, Elivan Silva Souza, Amanda Oliveira Lyrio, Sarah dos Santos Conceição, Ana Claudia Morais Godoy Figueiredo and Josicélia Estrela Tuy Batista contributed to the conception, article design, analysis and writing of the article;

Cauê Sousa Cruz e Silva, Luísa Caroline Costa Abreu, Ana Laura de Queiróz Pereira, Elaine Ramos de Moraes Rego and Delmason Soares Barbosa de Carvalho contributed to the planning and design of the article, review and final approval of the article;

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.

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

Revista de Epidemiologia e Controle de Infecção

Hospital Santa Cruz

ORIGINAL ARTICLE

Epidemiological model for the construction of scenarios of the dissemination of COVID-19 in Codó-MA

Modelo epidemiológico para construção de cenários da disseminação da COVID-19 em Codó-MA

Modelo epidemiológico para la construcción de escenarios de la diseminación del COVID-19 en Codó-MA

https://doi.org/10.17058/reci.v13i1.17853

Received: *08/22/2022*
Accepted: *11/28/2022*
Available online: *06/03/2023*

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ABSTRACT

Background and objectives: due to the increase in the number of cases of the new coronavirus in the city of Codó-MA, there was a need to carry out a study on the spread of COVID-19 in the municipality in order to have a better knowledge and understanding of the problem. A study was carried out on the spread of COVID-19 in the city of Codó-MA, comparing the quantitative data on the number of cases in 2020 and 2021 between May and July and using the epidemiological model Susceptible-Infectious-Isolated-Recovered (SIQR). **Methods:** we collected daily data from the epidemiological bulletins made available by the Municipal Health Department of Codó (SEMUS-Codó), we chose the SIQR compartmental model to carry out the simulations, we assumed hypotheses and estimated the parameters in order to design the scenarios. We simulated scenarios such as social distancing of healthy individuals and social isolation of infected individuals. **Results:** in early 2020, cases increased more frequently than in early 2021, and approximately 20% of those infected were in social isolation. According to projections, more than 80% of cases of COVID-19 were not accounted for in Codó. In 2021, there was greater underreporting than in 2020, approximately 82% and 85%, respectively. **Conclusion:** from the results, the authors conclude that the social isolation of those infected is a more efficient method to contain an epidemic than the total blockade of the population and that the high number of underreported cases is because most of these cases are asymptomatic.

Keywords: COVID-19. Physical Distancing. Sub-Registration. Social Isolation. Morbidity.

RESUMO

Justificativa e objetivos: devido ao aumento do número de casos do novo coronavírus na cidade de Codó-MA, viu-se a necessidade para fazer um estudo sobre a propagação da COVID-19 no município para a ter melhor conhecimento e entendimento do problema. Foi realizado um estudo sobre a disseminação da COVID-19

na cidade de Codó-MA, sendo comparados os dados quantitativos dos números de casos nos anos de 2020 e 2021 entre os meses de maio e julho e utilizando o modelo epidemiológico Suscetíveis-Infecciosos-Isolados-Recuperados (SIQR). **Métodos:** coletamos os dados diários dos boletins epidemiológicos disponibilizados pela Secretaria Municipal de Saúde de Codó (SEMUS-Codó), escolhemos o modelo compartimental SIQR para a realização das simulações, supomos hipóteses e estimamos os parâmetros para podermos projetar os cenários. Simulamos cenários, tais como distanciamento social dos indivíduos sadios e isolamento social dos indivíduos infectados. **Resultados:** no início de 2020, os casos aumentaram com mais frequência do que no início de 2021, e aproximadamente 20% dos infectados estavam em isolamento social. De acordo com as projeções, mais de 80% dos casos de COVID-19 não foram contabilizados em Codó. Em 2021, houve maior subnotificação do que em 2020, aproximadamente 82% e 85%, respectivamente. **Conclusão:** a partir dos resultados, os autores concluem que o isolamento social dos infectados é um método mais eficiente para conter uma epidemia do que o bloqueio total da população e que o alto número de casos subnotificados são porque a maioria desses casos são assintomáticos.

Descritores: COVID-19. Distanciamento Físico. Sub-Registro. Isolamento Social. Morbidade.

RESUMEN

Antecedentes y objetivos debido al incremento en el número de casos del nuevo coronavirus en la ciudad de Codó-MA, surgió la necesidad de realizar un estudio sobre la propagación del COVID-19 en el municipio con el fin de tener un mejor conocimiento y comprensión de el problema. Se realizó un estudio sobre la propagación del COVID-19 en la ciudad de Codó-MA, comparando datos cuantitativos del número de casos en 2020 y 2021 entre mayo y julio y utilizando el modelo epidemiológico Susceptible-Infeccioso-Aislado-Recuperado (SIQR). **Métodos:** recolectamos datos diarios de los boletines epidemiológicos que pone a disposición la Secretaría Municipal de Salud de Codó (SEMUS-Codó), elegimos el modelo compartimental SIQR para realizar las simulaciones, asumimos hipótesis y estimamos los parámetros para poder diseñar los escenarios. Simulamos escenarios como el distanciamiento social de personas sanas y el aislamiento social de personas infectadas. **Resultados:** a principios de 2020, los casos aumentaron con más frecuencia que a principios de 2021, y aproximadamente el 20% de los infectados se encontraban en aislamiento social. Según proyecciones, en Codó no se contabilizaron más del 80% de los casos de COVID-19. En 2021 hubo mayor subregistro que en 2020, aproximadamente 82% y 85%, respectivamente. **Conclusión:** de los resultados, los autores concluyen que el aislamiento social de los contagiados es un método más eficiente para contener una epidemia que el bloqueo total de la población y que el alto número de casos subregistrados se debe a que la mayoría de estos casos son asintomáticos.

Palavras clave: COVID-19. Distanciamiento Físico. Sub-Registro. Aislamiento Social. Morbosidad.

INTRODUCTION

Humanity has already gone through several epidemics, and at the end of 2019, in the city of Wuhan, China, a new viral infectious disease emerged that was designated by the World Health Organization (WHO) as COVID-19, caused by a virus called Severe coronavirus. Acute Respiratory Syndrome Coronavirus 2 of the Genus *Betacoronavirus* (SARS-CoV-2). In a short time, the virus spread around the world and, in early March 2020, it was already considered a pandemic.

Due to its rapid transmission, the first confirmed case in Brazil soon appeared, in São Paulo, on February 26, with a 61-year-old man who had a history of travel to Italy.[1] After confirmation of the first case, new cases appeared in all states of the country. The Ministry of Health recommended basic hygiene measures, such as washing the hands with soap and water and covering the mouth and nose when coughing or sneezing to avoid contamination. In Maranhão, the first case was confirmed on March 20 by the State Department of Health (SDH) in the city of São Luís. With the disease spreading throughout the territory, Codó soon had its first confirmed case on April 21, 2020, and since then, the numbers have only increased in the city.[2]

Regarding the rapid spread of the virus, several studies have been carried out to understand how its spread occurs and, consequently, find measures that help to control and contain its transmission.[3-7] One of the most used tools for this type of work are mathematical models, which have become important instruments in the analysis of the spread and control of infectious diseases. These models are strategies used to obtain some explanations and understanding of real situations, predicting important issues, such as changes caused by interventions in the spread of diseases.[8-10]

Many works were carried out with this same proposal; however, each city has its own population, cultural, social and economic reality. These factors contribute to the spread of a disease; Having said that, we sought to carry out a study of the city with our local reality that, since the first confirmed case of COVID-19, the numbers have grown rapidly. As it is a new, unknown disease and many cases are not serious, the population often does not take the necessary precautions. Therefore, there was a need to carry out a study on the spread of COVID-19 in the city of Codó to have better knowledge and understanding about the problems caused by the disease

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and to alert the population so that everyone can take the necessary precautions, whether through vaccines or protective measures. It is also expected that this research will be able to provide data to the health agencies of the municipality and that, through this information, it will help the administrative authorities to adopt the best strategies for controlling and eradicating the virus.

This research aimed to carry out a study on the spread of COVID-19 in the city of Codó-MA and compare the quantitative number of cases in 2020 and 2021 between May and July using the epidemiological model Susceptible-Infectious-Isolated-Recovered (SIQR).

METHODS

The chosen study site was the city of Codó located in the east of the state of Maranhão, with an estimated population (2021) of around 123,368 inhabitants, according to the Brazilian Institute of Geography and Statistics (IBGE - *Instituto Brasileiro de Geografia e Estatística*).[11] The period in which cases began to appear more frequently was from May 2020, therefore, May to July 2020 and 2021 were chosen for comparisons to be made.

All data collected from the daily newsletters are in the public domain and were found on social networks such as Facebook® and Instagram®, through the official page of the Municipal Health Department of Codó (SEMUS-Codó - *Secretaria Municipal de Saúde de Codó*), which contains information on accumulated confirmed, suspected, recovered and dead cases since the beginning of the pandemic. With these data, we applied the SIQR epidemiological model to compare the main changes in case numbers that occurred over a one-year period.

The model used was the SIQR epidemiological model. The SIQR model is an extension of the SIR model, and divides the population into four compartments that indicate the situation of each individual in relation to the development of the disease in each unit of time (t), namely: (S) individuals susceptible to being contaminated; (I) individuals who have been infected and can transmit the disease to susceptible individuals; (Q) individuals who acquired the disease and are isolated, i.e., they were diagnosed and are receiving treatment away from interaction with other people; and (R) individuals who have received treatment and are recovered. Therefore, the total population of the region under study can be written, which is represented by the constant N as the sum of all the compartments mentioned above,[2,4,7,11] namely:

$$N(t) = S(t) + I(t) + Q(t) + R(t) \quad (1)$$

The SIQR model is represented by a set of systems of ordinary differential equations:

$$\frac{dS}{dt} = -\alpha SI - \mu S \quad (2)$$

$$\frac{dI}{dt} = (1 - \phi_1)(1 - \eta)\alpha SI - (\gamma + \mu)I \quad (3)$$

$$\frac{dQ}{dt} = (1 - \phi_1)\eta\alpha SI - (\rho + \mu)Q \quad (4)$$

$$\frac{dR}{dt} = \phi_1(1 - \eta) + \phi_2\eta\alpha SI + \rho Q + \gamma I - \mu R \quad (5)$$

Therefore, α is the transmission rate; γ is the out-of-hospital recovery rate; μ is natural mortality rate; η is the rate of isolation of infectious individuals; ρ is recovery rate of individuals in quarantine; ϕ_{-1} is the mortality rate of non-isolated individuals; ϕ_{-2} is the mortality rate of isolated individuals. We denote that each equation represents the entry and exit of individuals from one compartment to another. As individuals enter a given compartment, the number increases, when they leave, the number decreases.

Assumptions about model

To carry out the simulations, some hypotheses were formulated about the model above and parameter estimates.

- We consider that not all people are equally likely to be infected;
- Susceptibility is the same for everyone, but for practical simulation purposes, we only consider a percentage of the susceptible population;
- To simulate mortality curves, assume that a rate of infected individuals will eventually die from the disease;
- The incubation period varies after exposure to the virus from 2 to 14 days;[12]
- We consider that people who test positive quickly have been isolated and are not likely to contaminate other individuals;
- We believe that, after recovery, individuals are immune to the disease, although there are cases of reinfection;

Parameter estimates

Based on the data collected and the hypotheses formulated, the parameter values were estimated to carry out the projections. Taking into account that the municipality of Codó is not very populous, there are about 123,368 inhabitants and a demographic density of 27.06 inhab./km², according to IBGE estimates.[11] It was considered that, when the virus reached its peak of contamination, it did not reach the entire population of Codó, due to its low demographic density. Therefore, we assume that not all population was susceptible. We consider that only 90% of the population was susceptible to being contaminated by COVID-19, i.e., 111,031 inhabitants.

After an individual is tested positive, they are quickly isolated and has no chance of contaminating other people, however there are indications that they can infect other individuals during this period.[13] Some studies point out that many cases are not notified, reaching 80% or more underreporting.[12-14] Therefore, we assume that the number of COVID-19 cases is much higher than the numbers confirmed by SEMUS-Codó and that only 20% of cases were legitimately registered; therefore, it was assumed that the rate of isolation of infectious individuals was η= 0.20.

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The fatality rate is the rate that calculates the proportion of the risk of death in the diagnosed infected population. In this work, the fatality rate provided by SEMUS-Codó in the months indicated for the study was used, which has an average of 3.94%. The mortality rate is the proportion of deaths in relation to all cases of infection, diagnosed or not. According to Bitar's study, the ϕ_{-1} mortality rate is 3.4%.[13] Therefore, to calculate the mortality rate of a fraction of isolated infected individuals, we use the following formula, according to the isolation rate of infected people η and the mortality rate of COVID-19:

$$\phi_2 = \frac{(0.0394 \,.\, 0.20 + \phi_1 .\, (\eta - 0.20))}{\eta} \quad (6)$$

As the infection rate of isolated people undergoing hospital treatment is already estimated, we estimate the recovery rate of individuals in hospital isolation or at home and, for that, we use the non-hospital recovery rate γ, which refers to a portion of the population who is not quarantined and who recovers on his own without medical treatments. We used the following formula:

$$\rho = \frac{1}{(1-\eta) \,.\, (3.5/0.20) + \frac{1}{\gamma}} \quad (7)$$

Regarding the natural mortality rate μ, as we do not have precise data for the city of Codó, we used the mortality rate for the state of Maranhão which, according to IBGE data, is equivalent to 0.00563%.[15]

One of the most important parameters in an epidemic is R_{-0} the average number of people that an infectious individual can infect during the period of disease infectivity, i.e., the time in which the infected can transmit the disease to the susceptible. if R_{-0}<1, the disease will not be able to spread on a large scale and will not reach the population; however, if R_{-0}<1, infected individuals infect more than one person on average and high contagion can occur among the population.[16] In this work, we used a value based on data made available by SEMUS-Codó, i.e., R_{-0}= 3.1.

The infection rate of α-susceptible individuals was assumed, through this rate we will know the number of healthy people who are contaminated in a time interval and the speed with which they pass from compartment (S) to class (I). Therefore, the following formula was used:

$$\alpha = \frac{\zeta R_0 \gamma}{N} \quad (8)$$

In order to know the number of healthy people who withdrew from interaction with society, we assume that a percentage of the population q strictly adhered to the recommendation to stay at home and the rest went about their lives normally. For this, we use the average number of people per family, according to IBGE, it has an average of 3.5 people per family.[15]

We consider that in each family all members adhered to the recommendation of social distancing, except for one, who continues to interact with people far from home anyway. For the part of the population that complies with strict distancing, we assume a basic reproduction number of 0.99 and for members who remain in contact with the society, we assume a basic reproduction number (0.99 + R_{-0})/2. We saw that α is sensitized by ζ, so the parameter ζ is defined as:

$$\zeta = \frac{\left(\frac{2.5q}{3.5} . 0{,}99 + \frac{q}{7} . (0.99 + R_0) + (1-q) . R_0\right)}{R_0} \quad (9)$$

It is important to emphasize that there is a difference between social isolation and social distancing: social isolation is carried out by those people who tested positive and were removed from interaction with society; social distancing is carried out by uninfected people who have decided not to interact with the population, i.e., they have stayed away from society on their own.[11]

Parameter analysis is the key piece for epidemiological modeling, because, through them, we discover the errors and uncertainties of collected data. According to table 1, we have a summary of all estimated parameters of the SIQR model.

Table 1. Estimated values for the parameters.

Parameters	Values	Meaning
N	111,031	Population susceptible to contagion
η	0.20	Isolation rate of infectious individuals
γ	1/14	Non-hospital recovery rate
μ	0.00563%	Natural mortality rate
ϕ_{-1}	3.4%	Mortality rate of non-isolated individuals
ϕ_{-2}	Equation (6)	Mortality rate of isolated individuals
R_{-0}	3.1	Amount that an infectious can infect other people
q	0.1 < 0.8	Percentage of isolation of the healthy population
ρ	Equation (7)	Recovery rate of individuals in isolation
A	Equation (8)	Infection rate of susceptible individuals
ζ	Equation (9)	Parameter sensitized by q

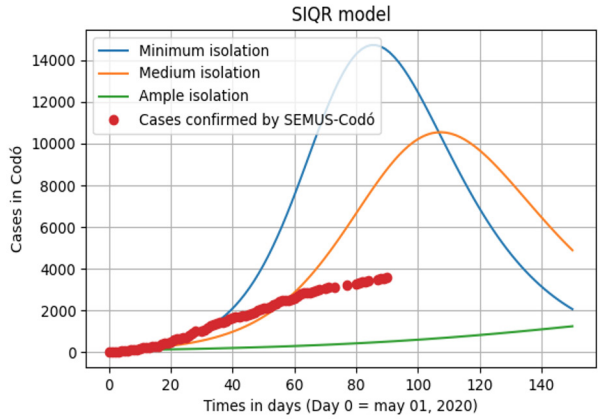
Different scenarios were used for the infected population and for the healthy population. We consider that a percentage of the infected population was isolated, namely: 20% is minimum isolation, which is the minimum number of infected people who can be confined; 40% is medium isolation, it is the mean isolation of the infected population who are away from social interaction; 80% is ample isolation, it is the highest value of infected people who can be removed from society.

For social distancing, we used the same values, 20%, 40%, and 80%, for minimum, medium, and ample distancing, respectively. However, in this other scenario, these values are for healthy people who decided to stay at home, not having contact with society.

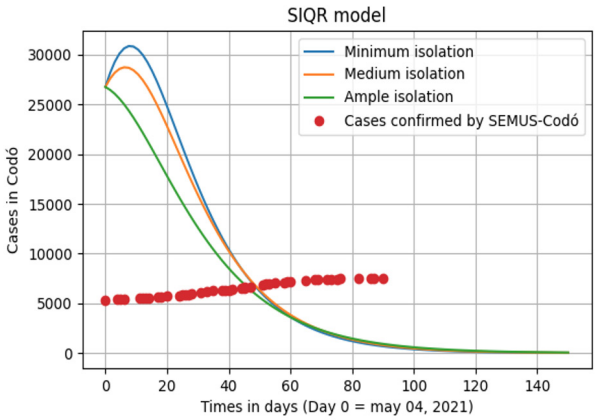
RESULTS

For the following projections, we consider different scenarios for the healthy population in social distancing, over a 150-day time frame. We estimated the basic reproduction number R_0=3.1 and the mean time of the infectious period in 14 days. In this simulation, we did not change the value of η, and only the value of q changed, as we can see in figure 1.

- In the first situation, we consider η equal to 0.20, i.e., 20% of the infected population was in social isolation and q equal to 0.20, i.e., 20% of the healthy population was in social distancing;
- In the second situation, we did not change the value of η, we kept it at 0.20 as previously mentioned and we considered q equal to 0.40, in other words, 40% of the healthy population was in distancing;
- In the third situation, we kept the value of η equal to 20% and assumed that q is 0.80, in other words, suppose that 80% of the healthy population was in distance.



(A)

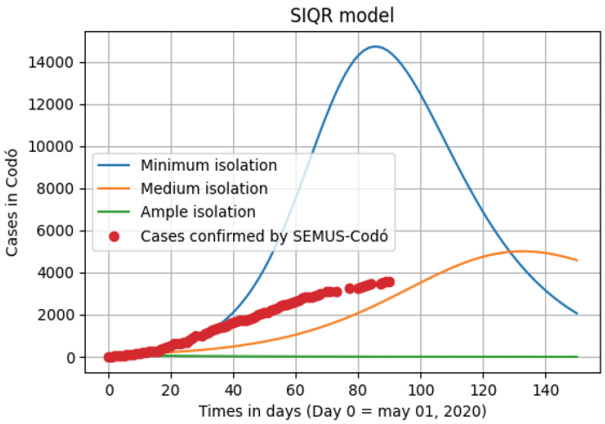


(B)

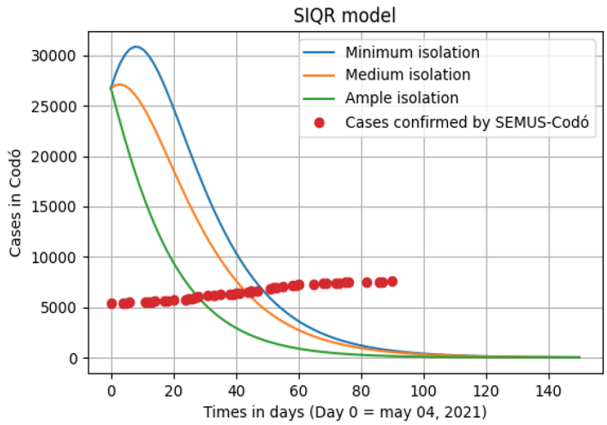
Figure 1. (A) Social distancing of healthy individuals vs number of infected individuals in 2020 over a period of 150 days. (B) Social distancing of healthy individuals vs number of infected individuals in 2021 in the period of 150 days.
Source: author.

In the following simulation, we reversed roles, keeping the rate of the healthy population in social distancing q at 0.20 and using other values for infectious individuals in isolation η. We maintained the basic reproduction number R_0=3.1 and the average time of the infectious period at 14 days, as shown in figure 2.

- q = 0.20, i.e., with this value, we consider that 20% of the healthy population is isolated and η equal to 0.20, i.e., 20% of the infected population was in social isolation;
- q = 0.20, again 20% of the healthy population is isolated and η equal to 0.40, therefore, 40% of the infected population was in isolation;
- q = 0.20, we kept the same value for the healthy population and η equal to 0.80, in other words, suppose that 80% of the infected population was isolated.



(C)



(D)

Figure 2. (C) Isolation of infected individuals vs healthy population in 2020 over a period of 150 days. (D) Isolation of infected individuals vs healthy population in 2021 within 150 days.
Source: author.

In Figure 3, we used all compartments in a 150-day scenario where 20% of the q healthy population was socially distancing and 20% of the infectious were isolated.

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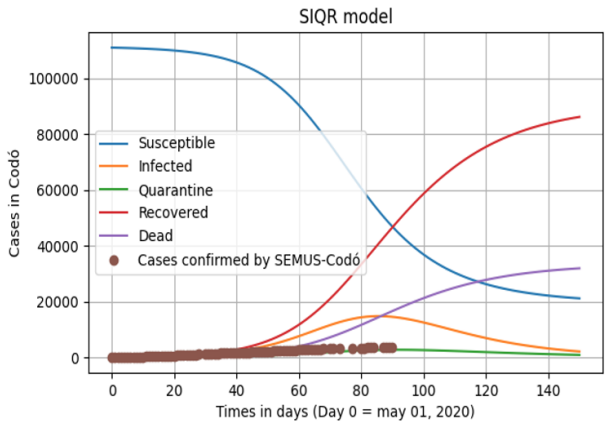
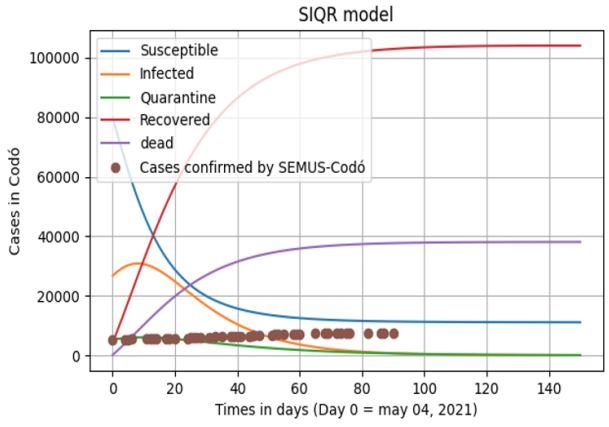


(E)



(F)

Figure 3. (E) Scenario involving all compartments of the SIQR model in the year 2020. (F) Scenario involving all compartments of the SIQR model in 2021.
Source: author.

DISCUSSION

According to projections, in figure 1(A),(B), approximately 20% of the healthy population in the period from May to July 2020 and 2021 were socially distancing and less than 20% of the infected population were socially isolated. In figure 2(C) and (D), both values are considered very low.[13] The ideal value for social isolation of the population would be 80%, however this percentage is impossible, because people need to leave home to work and survive, especially in the city of Codó, where there is a high poverty rate, since people social isolation measures affect the less financially favored classes more.

When we use social isolation at 20%, the virus reached its contamination peak around day 80, with approximately 15,400 cases. In figure 2(C), on that same date, the number of cases confirmed by SEMUS-Codó was 3,277, therefore, we can say that there were more or less 18,677 cases of COVID-19. The numbers confirmed by the secretariat represent 18% of the total amount, i.e., 82% of the cases of the new coronavirus were not accounted for on that date. There are many unreported cases because of the huge group of asymptomatic infected people.[12-14,17]

In an epidemic forecasting study in Shanghai, the rate of asymptomatic infections was very high, at around 90%.[18] Based on these works and projections, we can suggest that the factors that contributed to high underreporting were the large number of asymptomatic cases and the lack of rapid tests. Generally, rapid tests are mostly applied to symptomatic individuals, disregarding the huge potential for asymptomatic infected people, since the numbers of infected and unconfirmed cases grow faster than the number of confirmed cases.[12,17]

When we use 40% for healthy population in social distancing, as in figure 1(A), COVID-19 cases peaked with more than 10,000 cases, and when we put 40% for infectious population in isolation, the case numbers reached its peak with approximately 5,000 cases, as we can see in figure 2(C), with a large decrease in cases.

Already in ample isolation, when 80% of the infectious population is isolated, the numbers do not leave zero. In the previous simulation, we saw that when the distanced healthy population is 80%, cases reach just over 1,500. Thus, we observe that, with an increase in the infectious population in isolation, η directly leads to a lower growth of the compartment of infectious individuals (I) capable of spreading the disease and that the quarantine measure is more effective than the total blockade of the population.

Numerical results of quarantined individuals have a great influence on the transmission of COVID-19 infection. In this way, the minimization of transmission is related to the application of a quarantine policy.[19] The number of infected individuals can be reduced through mass testing, but the implementation of strict and immediate quarantine leads to reductions of about 90% in the total number of cases.[17]

It was observed that the numbers of cases of COVD-19 are much higher than those confirmed by SEMUS-Codó. Until May 11, 2021, the number of confirmed cases was 5,466. According to the simulations in Figure 2 (D), on the same date, the underreported cases were approximately 32,000. Adding this value, we have approximately 37,466, i.e., they were almost 7 times greater than those recorded by SEMUS-Codó. The 5466 represent approximately 15%, and the 32,000 underreported represent 85% of cases.

It can be seen that there was a large number of underreporting, and this can be explained because the rapid tests are mostly applied to symptomatic individuals. A study of unreported case estimation indicates that testing only symptomatic patients may overlook more than 50% of COVID-19 patients, who play an important role in transmitting the virus. It also suggests a scenario where placing only confirmed cases in quarantine is not able to prevent the spread of the virus due to the fact that there are a large number of undiagnosed cases. And the number of infected individuals can be reduced through mass testing.[17]

With all compartments of the SIQR model, Figure 3(E), initially, there are many susceptible people, becau-

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se, as the number of infected increases, the number of susceptible agents will decrease and, consequently, the number of recovered ones will increase.[19] We have seen that the number of underreported cases grows faster than the number of confirmed and isolated *q* individuals. This imbalance has been observed worldwide, with many undocumented cases of infection.[12-14,17]

As shown in figure 3(F), as of day 80, the entire population has already recovered and there are no more infectious agents to contaminate the susceptible, which also decreased significantly. As the percentage of circulation approaches zero, representing almost complete blockage, the number of cases tends to zero and stabilizes at a constant final value. In other words, the quarantine of those infected, symptomatic or not, contributes to the reduction of basic reproduction, reducing the rate of contamination.[4]

The predictions were very close to reality and were in line with the cases confirmed by SEMUS-Codó. In 2021, there was less spread than in 2020. Initially, cases increased very quickly and the government imposed protective measures such as social distancing, wearing masks and hand hygiene to contain the spread of the virus.

Between the months of May and July 2020 and 2021, we had no information regarding any case of the COVID-19 variant. The first dose of the vaccine started on January 21, 2021, and by the end of July 2021, only 14% of the population had taken the second dose. However, as the contamination peak had already occurred, the use of vaccine did not interfere with the simulations' value.

Based on the simulations, we concluded that increasing the amount of rapid testing in the entire population, with or without symptoms and stricter quarantine measures, would decrease a large amount of COVID-19 case numbers. However, the lack of resources is a challenging task for low-income countries or regions, resulting in a much smaller number of confirmed patients. Depending on the scenario, mass testing and strict quarantine measures could drastically reduce the total number of cases by 90% to 95%.[17]

The results found here may suffer interference from external agents, such as public managers, climatic and cultural, economic factors, etc. Please note that this is a 2020 and 2021 survey and results may be out of date. It would be interesting if future studies studied long-term sequels caused by COVID-19. We believe that the results of our study can provide guidance for coping with COVID-19 in the municipality.

ACKNOWLEDGMENTS

To the Scientific Initiation Research Group (PIBIC) of the *Universidade Federal do Maranhão*, Codó, for making the research available. To SEMUS-Codó, for having published data from the epidemiological bulletins.

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AUTHORS' CONTRIBUTIONS

Antonia Lisboa dos Santos contributed to the planning, conception, design of the article, interpretation of data and revision of the article.

Leonardo Rogerio da Silva Rodrigues contributed to the planning, article review and data interpretation.

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

Revista de Epidemiologia e Controle de Infecção

Hospital Santa Cruz

ORIGINAL ARTICLE

Epidemiological aspects of American and visceral cutaneous leishmaniasis in the city of Cametá, Pará, Amazon

Aspectos epidemiológicos da leishmaniose tegumentar americana e visceral na cidade de Cametá, Pará, Amazônia

Aspectos epidemiológicos de la leishmaniasis cutánea americana y visceral en la ciudad de Cametá, Pará, Amazonas

https://doi.org/10.17058/reci.v13i1.17333

Received: *02/15/2022*
Accepted: *04/15/2022*
Available online: *06/03/2023*

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ABSTRACT

Background and objectives: leishmaniases are anthropozoonosis considered a major public health problem in tropical regions and endemic in some areas of constant expansion. This study aimed to assess the main epidemiological aspects of American tegumentary leishmaniasis (ATL) and visceral leishmaniasis (VL) in the municipality of Cametá, in the state of Pará, from 2007 to 2017. **Methods:** this is a descriptive-exploratory analysis, of time series, with data collected in the Department of Epidemiological Surveillance of the Department of Sanitary Surveillance of Cametá. Statistical calculations were performed, and, for the coefficient of incidence of ATL and VL, the standard formula was used to obtain the indicator. **Results:** a total of 94 and 294 cases of ATL and VL were reported, with the highest incidence rate in 2008. The disease affected all established age groups, with high frequency in children under ten years of age for VL (n=174), and between 20 and 30 years of age, for ATL (n=71). The disease was more prevalent in males (ATL (89.4%) and VL (58.2%)), because men are more related to economic activities. **Conclusion:** considering the high number of rural cases, it is noteworthy that reporting in urban areas is also worrisome, in addition to the livelihood of local families, because it has made them vulnerable to the disease. Furthermore, there is concern about the possible expansion and change in the pattern of ATL in the municipality. The Municipal Department as well as the epidemiological surveillance must pay attention to promote investments and campaigns to combat and treat this important disease.

Keywords: *Epidemiology. Leishmania. Zoonosis. Amazon.*

RESUMO

Justificativa e objetivos: as leishmanioses são antropozoonoses consideradas um grande problema para a saúde pública em regiões tropicais e endêmicas em algumas áreas de constante expansão. Este estudo teve como

objetivo avaliar os principais aspectos epidemiológicos da leishmaniose tegumentar americana (LTA) e leishmaniose visceral (LV) no município de Cametá, no estado do Pará, no período de 2007 a 2017. **Métodos:** trata-se de uma análise descritiva-exploratória, de série temporal, com dados coletados no Departamento de Vigilância Epidemiológica da Secretaria de Vigilância Sanitária de Cametá. Realizaram-se os cálculos estatísticos, e, para o coeficiente de incidência de LTA e LV, utilizou-se a fórmula padrão para a obtenção do indicador. **Resultados:** foram notificados 94 e 294 casos de LTA e LV, com maior taxa de incidência em 2008. A doença atingiu todas as faixas etárias estabelecidas, com alta frequência nos menores de dez anos para LV (n=174), e, entre 20 e 30 anos de idade, para LTA (n=71). A doença foi mais prevalente no sexo masculino (LTA (89,4%) e LV (58,2%)), em virtude dos homens estarem mais relacionados com as atividades econômicas. **Conclusão:** em vista do alto número de casos rurais, ressalta-se que a notificação em área urbana também é preocupante, além dos meios de subsistência das famílias locais, pois vem tornando-as vulneráveis para o adoecimento. Ademais, há a preocupação com a possível expansão e mudança no padrão da LTA no município. A Secretaria Municipal, bem como de vigilância epidemiológica, deve atentar-se a promover investimentos e campanhas de combate e tratamento deste importante agravo.

Descritores: *Epidemiologia. Leishmania. Zoonose. Amazônia.*

RESUMEN

Justificación y objetivos: las leishmaniasis son antropozoonosis consideradas un importante problema de salud pública en las regiones tropicales y endémicas en algunas zonas de constante expansión. Este estudio tuvo como objetivo evaluar los principales aspectos epidemiológicos de la leishmaniasis tegumentaria americana (LTA) y la leishmaniasis visceral (LV) en el municipio de Cametá, en el estado de Pará, de 2007 a 2017. **Métodos:** se trata de un análisis descriptivo-exploratorio, de serie temporal, con datos recolectados en el Departamento de Vigilancia Epidemiológica de la Secretaría de Vigilancia Sanitaria de Cametá. Se realizaron cálculos estadísticos y, para el coeficiente de incidencia de LCA y LV, se utilizó la fórmula estándar para obtener el indicador. **Resultados:** se reportaron 94 y 294 casos de LTA y LV, con la mayor tasa de incidencia en 2008. La enfermedad afectó a todos los grupos de edad establecidos, con alta frecuencia en menores de diez años para LV (n=174), y entre 20 y 30 años. años de edad, para LTA (n=71). La enfermedad fue más prevalente en el sexo masculino (LTA (89,4%) y VL (58,2%)), debido a que los hombres están más relacionados con actividades económicas. **Conclusión:** dado el alto número de casos rurales, cabe señalar que la notificación en las zonas urbanas también es motivo de preocupación, además de los medios de subsistencia de las familias locales, ya que las ha vuelto vulnerables a la enfermedad. Además, existe preocupación por la posible expansión y cambio en el patrón de LTA en el municipio. La Secretaría Municipal, así como la de vigilancia epidemiológica, debe prestar atención a promover inversiones y campañas para combatir y tratar este importante problema.

Palabras clave: *Epidemiología. Leishmania. Zoonosis. Amazonas.*

INTRODUCTION

Leishmaniasis are anthropozoonosis considered a major public health concern in tropical regions.[1] They represent a set of diseases with important clinical spectra and epidemiological diversity, where, according to the Pan American Health Organization, it is estimated that 350 million people are exposed to risk, with records of approximately two million new cases per year in different forms.[2] Visceral (VL) and American tegumentary leishmaniasis (ATL) are classified as neglected diseases, caused by more than 20 species of leishmania.[3]

In the Amazon, there are two types of epidemic leishmaniasis: (cutaneous) ATL and (kala-azar) VL. ATL is characterized by cutaneous wounds that are located more frequently on uncovered parts of the body. In the future, wounds may appear on the mucous membranes of the mouth, nose and throat. This form of infection is known as "*ferida brava*" (in Portuguese), of an occupational nature, with reflections in the economic and social field, as it is directly related to rural activities in enzootic regions.[4] On the other hand, VL is a systemic disease, since it affects several internal organs, which is characterized by irregular episodes of fever, spleen and liver swelling, in addition to substantial weight loss and anemia (severe condition), responsible for due to high mortality rates in underdeveloped countries, marginalized populations and contributing to perpetuate cycles of poverty and social exclusion.[5]

Transmission occurs through the bite of infected female sandflies, belonging to the genus *Lutzomyia*, with emphasis on the species *Lutzomyia longipalpis* (*Lu. longipalpis*), the main species involved in the transmission of etiological agent *Leishmania chagasi*, which causes VL; and *Leishmania amazonenses, Leishmania guyanensis, Leishmania braziliensis*, main species causing ATL in Brazil.[6,7] The transmitting insects belong to the order *Diptera*, suborder *Nematocera*, family *Psychodidae* and subfamily *Phlebotominae*.[8] Sandflies, vectors of leishmaniasis, are also popularly known in some regions as "*mosquito palha*", "*birigui*", "*flebótomo*", "*ligerinho*", among others.[9]

In recent decades, epidemiological analyzes suggest changes in the disease transmission pattern, with high endemicity in practically deforested rural areas, and

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in peri-urban regions.[10] The infection dynamics differs between the places of occurrence due to variables such as vectors, parasites, ecosystems, in addition to social processes of production and land use.[10]

Although the epidemiological and landscape characteristics of these places are similar, they constitute areas where the forms of space occupation and land use interfere with socioecological processes, which result in instability in ATL incidence.[11]

VL diagnosis can be performed using immunological and parasitological techniques, such as the detection of anti-Leishmania antibodies, indirect immunofluorescence reaction and rapid immunochromatographic test.[12] In 1913, the first necropsy case of a patient born in Boa Esperança-MG was described. Since then, it has been reported in several Brazilian municipalities, showing differences in transmission pattern, initially at a higher rate in wild and rural environments and more recently reported in urban centers.[13]

In 2016, Brazil registered 12.690 cases of VL, the highest rate among American countries, followed by Colombia (10.966), Nicaragua (5.423) and Peru (7.271), together accounting for 74.3% of total records.[2] The incidence rate in the following year decreased, with an incidence of 1.98 cases per 100.000 inhabitants.[14] In the Brazilian Amazon, between 1975 and 2015, there was a great disease expansion and incidence. According to the Unified Health System Department of Informatics System (DATASUS - *Departamento de Informática do Sistema Único de Saúde*), in the same period, in the state of Pará, 3.882 cases of ATL were registered in the Notified Diseases Information System (SINAN - *Sistema de Informação de Agravos de Notificação*).[14]

Considering the importance of ATL and VL in the Amazonian context, in Cametá-PA, whose municipality is in a constant process of expansion, it becomes relevant to better understand the dynamics of transmission of this parasitic infection, which is very present in the region. Thus, this study aimed to assess the main epidemiological aspects of ATL and VL in the municipality of Cametá, in the state of Pará, from 2007 to 2017, in order to verify the population's vulnerability aspects.

METHODS

The study carried out was of the descriptive-exploratory type, carried out through a survey of secondary data collected at the Department of Epidemiological Surveillance of the Department of Health Surveillance (DHS) of Cametá-PA. Data show the prevalence of human ATL and VL by year, sex, age group, area of residence and number of cases and the incidence coefficient, from 2007 to 2017.

The municipality of Cametá is located in the state of Pará, northern Brazil, with an estimated population of 140,814 inhabitants, and demographic density of 39.23 inhab./km^2, with an area of 3,081.367 Km^2.[16] The average local temperature is 26.9 °C, with a precipitation rate of 55 mm in dry months and 420 mm in rainy months.[16]

Statistical calculations were performed using Microsoft Office Excel 2019, to obtain the frequency in percentage (%), and for the incidence coefficient (I.C.) of ATL and VL, the standard formula for obtaining the indicator was used, the starting from the number of cases of leishmaniasis: I.C. = Number of new cases of leishmaniasis x 100,000 inhabitants/population.

All data officially cataloged in the DHS database of the Ministry of Health were included, with link: https://www.gov.br/saude/pt-br/composicao/svsa.

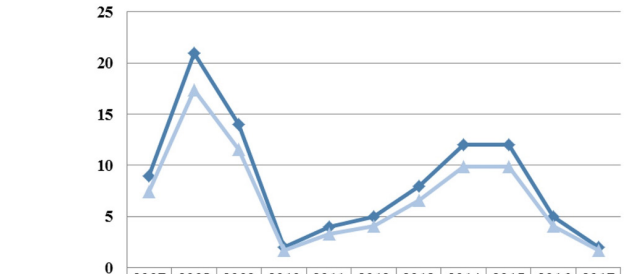
A survey was carried out in cartographic databases of the Brazilian Institute of Geography and Statistics (IBGE - *Instituto Brasileiro de Geografia e Estatística*) and Cartography of the Brazilian Amazon. For the spatial analysis technique, Google Earth Pro was used, which allows the visualization of real images captured by satellite, based on the Geocentric Reference System for the Americas (SIRGAS - *Sistema de Referência Geocêntrico para as Américas*) 2000.

Due to the use of freely accessible secondary data and without any identification of the research subjects, submission and approval by an ethics committee was not necessary, as defined by Resolution of the Brazilian National Health Council 510 of April 7, 2016: https://conselho.saude.gov.br/resolucoes/2016/Reso510.

RESULTS

American cutaneous leishmaniasis

During the study period, 94 cases of ATL were found, oscillating over the 11 years. There was a variation in the incidence rate, reaching a maximum peak in 2008, with a rate of 17.37 per 100.000 inhabitants, and a minimum in 2010 and 2017, with 1.65 per 100.000 inhabitants (Figure 1).



	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
N° of cases	9	21	14	2	4	5	8	12	12	5	2
I. C.	7.4	17.4	11.6	1.7	3.3	4.1	6.6	9.9	9.9	4.1	1.7

Figure 1. Number of cases and incidence coefficient of American tegumentary leishmaniasis in the municipality of Cametá, Pará, from 2007 to 2017.
*Source: Notified Diseases Information System, Department of Health Surveillance of Cametá. *Number of cases; **I.C.- incidence coefficient.*

The disease affects all established age groups, with low frequency in children under five years of age, however, tending to increase progressively as age advances, with a higher frequency among individuals between 20 and 30 years of age, male, coming from rural space (Table 1).

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Table 1. Behavior of American tegumentary and visceral leishmaniasis in the municipality of Cametá-PA, between 2007 and 2017.

	ATL		VL	
Characteristic	**N° of cases**	**%**	**N° of cases**	**%**
Sex				
Male	84	89.4	171	58.2
Female	10	10.6	123	41.8
Age range				
<1	1	1.1	24	8.2
1-4	3	3.2	117	39.8
5-9	4	4.2	57	19.4
10-14	4	4.2	21	7.1
15-19	11	11.7	19	6.5
20-29	20	21.3	28	9.5
30 and +	51	54.3	28	9.5
Zone of residence				
Urban	22	25.9	22	19.5
Rural	63	74.1	63	80.5

Source: Department of Health Surveillance, Cametá, 2018.

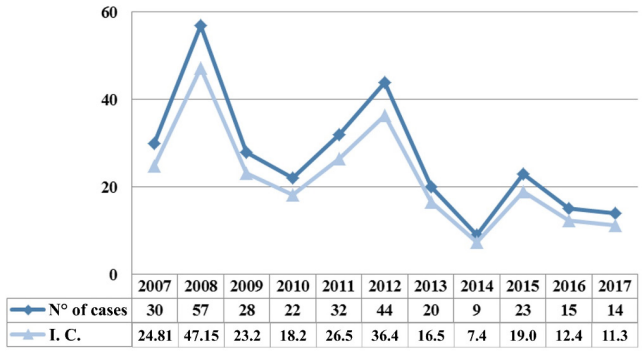
According to the survey, the largest reported cases of ATL were in the rural area, aged between 20 and 30 years. Santos et al.,[18] when carrying out an epidemiological study in the state of Alagoas, observed that 39% of cases were ATL, with a prevalence in people aged between 20 and 49 years, corroborating with those found in this research.

Figure 2 shows the five central districts (Castanhal, Bairro Novo, Primavera, Bom Jesus and São Raimundo) of the municipality as possible areas of vulnerability, which allows identifying probable points of urban leishmaniasis infections according to the epidemiological survey.

Visceral leishmaniasis

During the study period, 294 cases of VL were reported in the municipality of Cametá, with the highest occurrence between 2007 and 2012 (figure 3). The lethality rate in the period was 1.7% (five deaths), with higher and lower incidence records in 2008 and 2009, with 47.2 and 7.44 cases per 100.000 inhabitants, respectively.

Among the reported cases, there was a higher frequency in males (Table 1). As for the age group variable, the most affected by VL were children between 1 and 9 years old, with 39.8% of cases between 1 and 4 years old, which refers to greater vulnerability in this phase of life.



	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
N° of cases	30	57	28	22	32	44	20	9	23	15	14
I. C.	24.81	47.15	23.2	18.2	26.5	36.4	16.5	7.4	19.0	12.4	11.3

Figure 3. Number of cases and coefficient of incidence of visceral leishmaniasis in the municipality of Cametá, Pará, from 2007 to 2017.
*Source: Notified Diseases Information System, Department of Health Surveillance of Cametá. *Number of cases; **I.C.- incidence coefficient.*

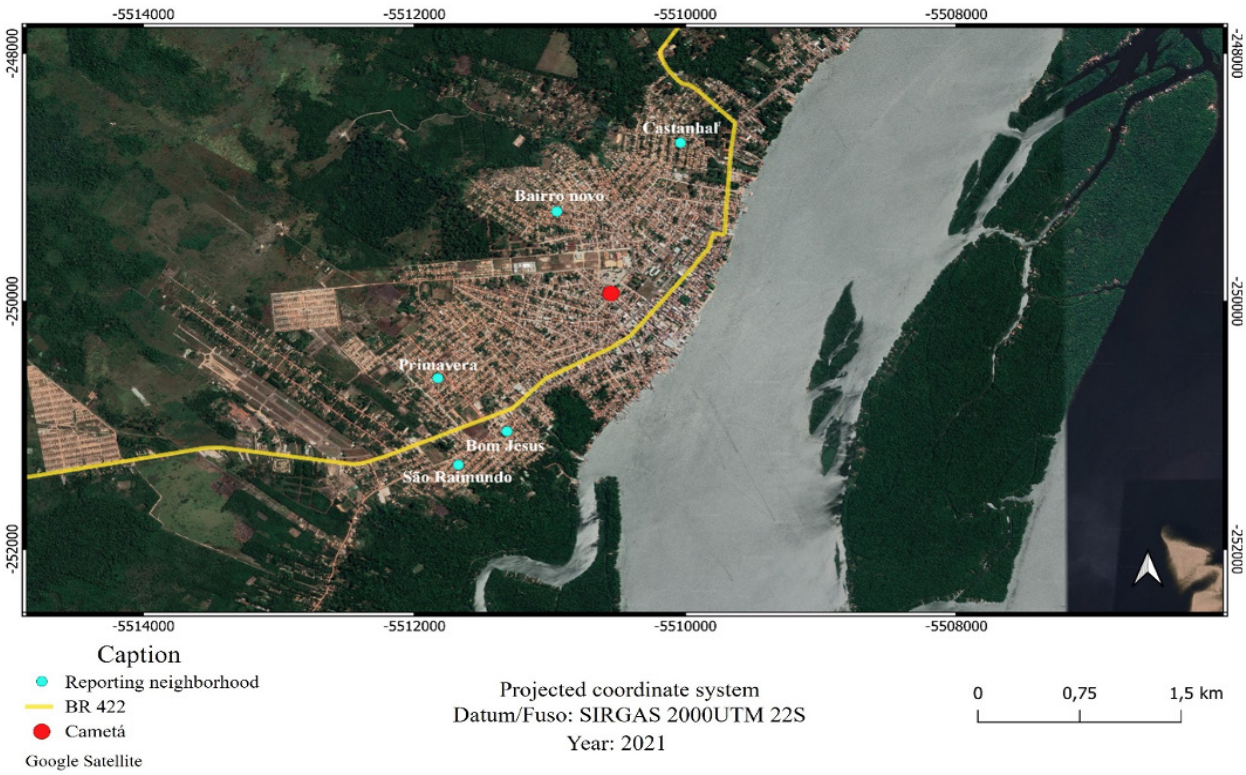


Figure 2. Probable areas of American tegumentary leishmaniasis infections in Cametá-PA.
Source: Department of Epidemiological Surveillance of the Department of Health Surveillance. Cametá and Google Earth, 2021

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DISCUSSION

During the study, a decline in the incidence rate of cases was observed. I.C. use (Figure 1) better assesses the risk of acquiring the disease in the locality.[16] Thus, according to I.C. the risk of acquiring the disease in 2017 was lower compared to previous years, as it presented a rate of 1.65 per 100.000 inhabitants, the same value recorded in 2010.

According to data from the Pan-American Health Organization,[19] Brazil recorded a total of 12,690 cases of leishmaniasis in 2016, a reduction of 34% compared to the previous year.

The highest number of cases was concentrated between 2008 and 2009, with 21 and 14 cases, respectively. In subsequent years, there was a decrease, but the curve remained stable, rising again in 2014 and 2015. It assumes that this high incidence is related to work activities carried out in regions, such as prospecting activities, agriculture, wood exploitation, agrarian settlements close to forest areas (large scale), deforestation for implementing pastures, in addition to the favorable climatic conditions for the vector development.[18]

ATL has three transmission patterns: wild – anthropic actions bring man closer to the forest, habitat of wild animals; occupational - occurs in areas of exploitation of forests related to deforestation and construction; and rural or peri-urban - related to migratory areas and occupations in urban regions, close to secondary forests[19], which refers to pattern transmission of the city of Cametá, since it presents characteristics of territorial expansion and similar socioeconomic activities.

The increase in cases of ATL in males observed in the present study is concentrated among young people and adults, who are in productive phase, who carry out deforestation and/or reforestation activities, in addition to agricultural practices and logging, road construction, subdivisions, activities in tropical forests, communities adjacent to forests, among others.[20] In an analysis in Petrolina-PE, similar results were also obtained regarding the higher incidence rate in economically active men, as it is linked to the fact that these are more present in places outside the home.[21]

Regarding disease transmission in women, older adults and children, it can be related to the adaptation of the vectors to the poorest households, with a deficiency in water supply, garbage collection, in addition to living with domestic animals.[22] It assumes that the drop in the number of cases, mainly in children, is due to the fact that they have remained on a smaller scale in forest environments, in addition to underreporting, culminating in flaws in the municipality's current epidemiological situation. However, despite the low records of VL among female individuals, these are not exempt from infestations, since in socioeconomically precarious areas they become propitious due to invasions in the indoor environment, such as contaminated dogs.[22] Studies highlight a significant number of cases of the disease in women and children in different regions of South America, which is an indicator of intra and peridomestic vector circulation.[23]

The illness process depends solely on the vector and a host/reservoir. Changes in the natural landscape, environmental degradation with loss of vegetation cover are the key to the responses of the large number of cases in these localities.

As for ATL, 25.9% of cases were reported in urban areas, which demonstrates an expansion of the disease dynamics throughout the territory. When verifying the vulnerability of the urban population of Araguaína, it was observed that 30% of cases of leishmaniasis were in the city, with a prevalence in those aged 60 years or more.[21] Spatial distribution of cases in humans suggests that the epidemic process is in motion, due to the displacement of populations from wild reservoirs to areas close to homes in search of survival.[23] A common characteristic observed is that, in the neighborhoods where the infections are present, they are close to primary and/or secondary forest areas of the legal Amazon, which is in line with specialized literature.[12]

As for the most affected age group being among people from 20 to 30 years old, a different result is demonstrated, if compared with other studies in the extreme north of Brazil, in which the highest occurrence was among children under 10 years of age (86, 8%), with a second peak in the age group of 20 to 29 years (5.1%). Another similar data is that of Alagoas, which, according to an epidemiological survey between 2013 and 1017, 39% of ATL cases were in individuals aged between 20 and 49 years.[18]

According to figure 3, two peaks of the disease are observed, with the highest occurring in 2008 and another in 2012. Similar studies such as those by Temponi,[24] when assessing ATL spatial circuits in Minas Gerias, obtained outbreaks of the disease in the same period.

There was a decline in the incidence coefficients and low lethality rate in the sample municipality. A similar case occurred in an epidemiological study in Barcarena, Pará, between 2004 and 2008, due, in part, to the intensification of local surveillance actions, such as the expansion in the coverage of health units and investments in the structuring of programs to combat VL. The Ministry of Health also presented similar results when assessing the epidemiological situation of VL in the country in 2017.[10]

It was possible to verify that children aged between 1 and 9 years were the most vulnerable in the analyzed period, 59.2% of the cases, since they are more exposed to the vector in the peridomicile, so common in endemic areas, in addition to their relative immunological immaturity cell, aggravated by the malnutrition of economically poor populations.[25]

Regarding patients' residence, 80.5% live in rural areas. According to epidemiological records, the infection was more prevalent in rural areas, demonstrating an endemic nature in these regions. VL is a neglected disease of neglected populations. Factors such as poverty, migration, unplanned urban occupation, environmental destruction, precarious sanitation/housing conditions and malnutrition are some of the determining factors.[26]

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The municipality's economic base is agriculture, extraction works and fish farming, present both in families in island areas and in urban centers. The rural population represents a significant portion in the municipality of Cametá, corresponding to 56.30% of the total, with 70.96% living below the poverty line.[19] These individuals, in addition to living and working in forested regions, carry out agriculture and family livestock activities, and thus consequently are vulnerable to bites by transmitting vectors. Due to agrarian changes in recent decades, today 85% of the population lives in urban areas, leading to the emergence and re-emergence of parasitic diseases, including VL.[24]

It is also important to emphasize that, despite the rural character, 19.5% of cases still occur in the urban area, showing the expansion and urbanization of VL. For the Brazilian Society of Tropical Medicine, the domestic dog is the main reservoir-transmitter in the urban environment as well as the sand fly (*Lutzomyia longipalpis*), the latter of greater epidemiological importance.[25] The pillars of the current Visceral Leishmaniasis Control Program (PVCVL - *Programa de Controle da Leishmaniose Visceral*) are established in Ordinance 1.399 of December 15, 1999, emphasizing early diagnosis, as well as treatment of human cases, through the reduction of sandfly populations and elimination of infected reservoirs.

In view of this, laboratory diagnosis methods are emphasized, as they are important not only for confirming clinical findings, but also provide epidemiological information, through the identification of circulating species, which are fundamental to direct combat and control measures.

Based on this, the study provided knowledge of ATL and VL in the municipality of Cametá, pointing out the main epidemiological characteristics of the disease. In both diseases, males were the most affected, residents of rural spaces who carry out field activities. As for age, ATL was predominant among individuals between 20 and 30 years of age, as they are economically active, something different from VL's behavior, with a higher occurrence in those younger than 10 years of age.

With such findings, it is possible to bring more visibility to this population that is vulnerable to the disease and, from this, propose more effective solutions to local secretariats, with the aim of intervening in the high curve of cases.

Preventive actions are necessary for the Cametá community, in order to keep the population informed about leishmaniasis, promoting, together with public health agencies, the fight against transmission of the vector in the region. Given the high number of cases not only in the rural area, but also in urban centers, it is emphasized that disease reporting is of great concern, thus characterizing a possible expansion in the dynamics of leishmaniasis in the municipality.

Considering the high number of rural cases, it is noteworthy that reporting in urban areas is also worrying, in addition to the means of subsistence of local families, as it has been making them vulnerable to illness. Moreover, there is concern about the possible expansion and change in ATL pattern in the municipality. The Municipal Department of Health as well as the epidemiological surveillance department must pay attention and promote campaigns to combat and treat this important public health problem, as well as investments and actions of public management policies. Preventive work for the Cametá community is of paramount importance in order to keep the population informed about leishmaniasis, which historically plagues the region.

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AUTHORS' CONTRIBUTIONS

Lucas Henrique da Silva e Silva, Marcelo Coelho Simões and Beatriz Oliveira Miranda contributed to article conception, design, analysis and writing;

Cléa Nazaré Carneiro Bichara and Jéssica Herzog Viana contributed to article planning, design, review and final approval.

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

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

Revista de Epidemiologia e Controle de Infecção

Hospital Santa Cruz

ORIGINAL ARTICLE

Epidemiology of clinical complications of accidents caused by venomous animals in Brazil

Epidemiologia das complicações clínicas de acidentes provocados por animais peçonhentos no Brasil

Epidemiología de las complicaciones clínicas de accidentes causados por animales venenosos en Brasil

https://doi.org/10.17058/reci.v13i1.17696

Received: *06/06/2022*
Accepted: *14/08/2022*
Available online: *06/03/2023*

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ABSTRACT

Background and objectives: Accidents caused by venomous animals, included in the set of Neglected Tropical Diseases, often evolve to local and systemic clinical complications related to increased morbidity and mortality and saturation of health care resources. This study aimed to analyze the epidemiological profile, spatial distribution and temporal trend of clinical complications caused by accidents with venomous animals in Brazil. **Methods**: This is a quantitative, cross-sectional, observational, epidemiological study of the clinical complications of accidents caused by venomous animals reported to the Notifiable Diseases Information System from 2007 to 2019. **Results**: Of the 2,164,645 evaluated notifications, 38,934 cases (1.8%) showed complications. We observed a higher proportion of clinical complications (per 1,000 total cases) among men, Indigenous individuals, illiterates, and victims who received care 24 hours after their accidents, and snakebites. We also found a higher proportion of clinical complications among severe cases (198.8), cases treated with serum therapy (45.7), and those that resulted in death (41.8). The annual incidence of complicated cases increased, especially in the Brazilian Southeast region (+67.2%). The proportion of clinical complications is more worrying in the states of Amazonas, Rondônia, Amapá, and Pará. **Conclusion**: This study found a higher proportion of clinical complications among men, Indigenous people, illiterates, residents of rural areas, victims of snake bites, those who received late medical and hospital care, those who needed serum therapy, and individuals who had death as their outcome. We found a more severe spatial distribution of the annual incidence of complicated cases in the states of Amazonas, Rondônia, Amapá, and Pará, and that the tendency of the annual incidence of clinical complications increased more sharply in the Brazilian Southeast region.

Keywords: *Animals Poisonous. Epidemiology. Health Information Systems. Public Health Surveillance.*

RESUMO

Justificativa e objetivos: Os acidentes causados por animais peçonhentos, incluídos no conjunto de Doenças Tropicais Negligenciadas, predispõem a evolução de complicações clínicas locais e sistêmicas, relacionadas ao aumento da morbimortalidade e a saturação dos recursos assistenciais em saúde. Têm-se como objetivo analisar o perfil epidemiológico, a distribuição espacial e a tendência temporal das complicações clínicas causadas dos acidentes por animais peçonhentos no Brasil. **Métodos:** Estudo epidemiológico observacional transversal quantitativo das complicações clínicas dos acidentes causados por animais peçonhentos notificadas ao Sistema de Informação de Agravos de Notificação entre 2007-2019. **Resultados:** De 2.164.645 notificações, 38.934 casos (1,8%) apresentaram complicações. Observou-se maior proporção de complicações clínica (por 1.000 casos totais) em indivíduos do sexo masculino, indígenas, analfabetos, atendimentos realizados após 24h e vítimas de ofidismo. Ainda, a proporção de complicações clínicas foi maior entre os casos graves (198,8), os receptores de soroterapia (45,7) e os óbitos (41,8). A incidência anual de casos complicados ascende principalmente na Região Sudeste (+67,2%). A proporção de complicação clínica é mais preocupante nos estados do Amazonas, Rondônia, Amapá e Pará. **Conclusão:** O presente estudo identificou maior proporção de complicações clínicas entre pessoas do sexo masculino, indígenas, analfabetos e moradores de zona rural, cujo acidente ocorreu por picada de serpentes, que tiveram atendimento médico-hospitalar retardado, que necessitaram de soroterapia e que tiveram o óbito como desfecho. A distribuição espacial da incidência anual de casos complicados assevera-se nos estados do Amazonas, Rondônia, Amapá e Pará e a tendência da incidência anual de complicações clínicas ascende mais na Região Sudeste.

Descritores: *Animais Peçonhentos. Epidemiologia. Sistemas de Informação em Saúde. Vigilância em Saúde Pública.*

RESUMEN

Justificación y objetivos: Los accidentes causados por animales venenosos, incluidos en el conjunto de Enfermedades Tropicales Desatendidas, predisponen a la evolución de complicaciones clínicas locales y sistémicas, relacionadas con el aumento de la morbimortalidad y la saturación de los recursos asistenciales. El objetivo es analizar el perfil epidemiológico, la distribución espacial y la tendencia temporal de las complicaciones clínicas causadas por accidentes con animales venenosos en Brasil. **Métodos**: Estudio epidemiológico, observacional, transversal y cuantitativo de las complicaciones clínicas de los accidentes por animales venenosos notificados al Sistema de Información de Enfermedades de Declaración Obligatoria entre 2007-2019. **Resultados**: De 2.164.645 notificaciones, 38.934 casos (1,8%) presentaron complicaciones. Se observó una mayor proporción de complicaciones clínicas (por 1.000 casos totales) en varones, indígenas, analfabetos, cuidados posteriores a las 24 horas y en víctimas de mordeduras de serpientes. Además, la proporción de complicaciones clínicas fue mayor entre los casos graves (198,8), los receptores de sueroterapia (45,7) y las muertes (41,8). La incidencia anual de casos complicados aumentó principalmente en la región Sudeste (+67,2%). La proporción de complicaciones clínicas es más preocupante en los estados de Amazonas, Rondônia, Amapá y Pará. **Conclusión:** Este estudio identificó una mayor proporción de complicaciones clínicas entre varones, indígenas, analfabetos y residentes de zonas rurales, que tuvieron el accidente a causa de mordeduras de serpientes, que tuvieron retrasada la atención médica y hospitalaria, que necesitaban sueroterapia y que tenían la muerte como resultado. La distribución espacial de la incidencia anual de casos complicados se afirma en los estados de Amazonas, Rondônia, Amapá y Pará, y la tendencia de la incidencia anual de complicaciones clínicas se eleva más en la región Sudeste.

Palabras clave: *Animales Venenosos. Epidemiología. Sistemas de Información em Salud. Vigilancia de la Salud Pública.*

INTRODUCTION

The Brazilian Notifiable Diseases Information System (SINAN)[1] recorded 2,691,447 accidents by venomous animals between 2007 and 2022. Such incidents kill more than 500,000 people and cause disabilities in many more every year worldwide.[2]

These accidents violate third-generation human rights as they stem from a compromised environment and the rupture of the ideal of solidarity and socioeconomic equality. Thus, they are included in Neglected Tropical Diseases.[3] Global public health authorities argue that this problem is associated with poverty, precarious public services, health vulnerability, and the hot and humid climate of tropical countries.[4, 5]

This led to the inclusion of these accidents in Brazilian List of Compulsory Notification, in accordance with Ordinance No. 2,472 of August 31, 2010, later updated by the Ministry of Health Ordinance No. 264 of February 17, 2020.[6] SINAN, an important ecological, medical, and economic device since it aggregates public health data,[6] began reporting these occurrences to the Ministry of Health.

Venomous animals have glands that produce toxic substances and mostly enzymatic solutions for defense and hunting,[7] using their teeth, chelicerae, and stingers or by contact.[8, 9] Case courses vary, and they often evolve to local and/or systemic clinical complications.

Out of the diversity of the Brazilian fauna, some venomous animals stand out for the frequency and severity

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of the accidents they cause, such as *Lonomia* caterpillars, which may cause hemorrhagic syndrome; *Bothrops, Crotalus, Lachesis*, and *Elapidae* snakes, which may then evolve to acute renal failure, paralysis, neuroparalysis, and hemorrhage; *Tityus serrulatus* (Lutz & Melo, 1922), *Tityus bahiensis* (Perty, 1833), and *Tityus stigmurus* (Thorell, 1876), whose venom can cause seizures, pulmonary edema, cardiogenic shock, and heart failure; and *Loxosceles* spiders, which can cause cardiac arrhythmias and shock.[9]

Accidents are classified according to their severity, i.e., if they offer clinical conditions with self-limited transient symptoms, prolonged ones, or the risk of death.[10] Thus, victims have several prognoses, including permanent or temporary morbidities and death.

Further evaluating these events is essential to delineate and strengthen strategies to rationalize the distribution of immunobiologicals to affected areas according to their vulnerability – proportional to the qualitative analysis of reports, as per Ordinance No. 1.138/GM/MS of May 23, 2014, and Information Note No. 74/2016 - CGPNI/DEVIT/SVS/MS.[11, 12]

As we recognize its social relevance as a public health problem, this study aimed to analyze the epidemiological profile, spatial distribution, and temporal trend of complications due to accidents by venomous animals in Brazil.

METHODS

This is an individual, quantitative, observational, cross-sectional, and epidemiological study whose assessed population was composed of all reported accidents due to venomous animals in Brazil between 2007 and 2019. Data from the Brazilian Ministry of Health Surveillance Secretariat were collected via SINAN.

All accidents by venomous snakes, scorpions, spiders, caterpillars, and bees in all national federative units were included. The evaluated period was chosen by inserting accidents by venomous animals as neglected diseases from 2007 to 2019 (given the available of data on SINAN). Cases without occurrence site and year and/or showed less than 80% of the chosen analysis variables were excluded.

Analysis variables were divided into a) sociodemographic data (gender, skin color, and educational attainment); b) accident circumstances (geographical area, time elapsed until care administration, attacked anatomical region, accident type, case classification, serotherapy, amount of used immunobiological ampoules, relation with victims' work, and case evolution); and c) occurrence measures (incidence and prevalence of total and complicated cases and the proportion of clinical complications).

The total number of reported cases was individually analyzed and the occurrences that met our inclusion criteria composed a database on Statistical Package for the Social Sciences (SPSS), version 21, by IBM.[13] The consistency and normality of its variable distribution was evaluated by the Kolmogorov-Smirnov test. Variables were then descriptively and statistically analyzed and absolute and relative frequencies and central tendency and dispersion, distributed. The proportion of clinical complications was obtained by multiplying the ratio between the number of complicated cases and the total number of cases by 1,000.

Temporal trend analysis was performed using polynomial regression, which was tested for linear, quadratic, cubic, and exponential models. Our final model depended on statistical significance, the highest coefficient of determination (r^2), and final adequacy in relation to how notifications tended to behave graphically over time. Thus, models whose probability of type-I error (alpha) remained below 5% were considered statistically significant.

Spatial analysis was carried out using TABWIN, version 4.15, maps of Brazil, and adopting Brazilian federative units and municipalities as reference units. This study dispensed with approval from a Research Ethics Committee as it is based on secondary public records which omit personally identifiable information.

RESULTS

Brazil recorded 2,164,645 accidents by venomous animals from 2007 to 2019, of which 38,934 showed some type of clinical complication, totaling 17.9 complications per 1,000 cases.

Illiterates (30.0), Indigenous individuals (48.5), men (21.0), and rural inhabitants (26.6) showed a higher proportion of clinical complications per 1,000 cases. We found more severe complications if victims received care 24 hours or more after the accident (70.5) (Table 1).

Injured legs and *Lachesis* accidents showed complications more often. Our sample highlighted severe cases, those which required serotherapy, and deaths due to accidents with venomous animals.

The temporal trend for the annual incidence of total cases (AITC) decreased in the Brazilian Northeast (-63.36), Southeast (-44.83), and Midwest (-58.18) regions, increasing in the North (+55.78) and South (+16.81) (Table 2 and Figure 1). The annual incidence of complicated cases (AICC) decreased in the North, but increased in the Southeast. We should also highlight the increase in the AICC in Northeast (+9.30%) and Midwest (+56.48%) regions, although we found no statistical significance in the tested models, which showed $p>0.05$, as shown in table 2.

Note that the states of Alagoas, Tocantins, Minas Gerais, and Paraná showed a higher prevalence of total cases, and Amazonas, Rondônia, Amapá, and Pará, the highest proportion of clinical complications (Figure 2).

The percentage of the average use of all immunobiological types to manage cases increased due to case complications, as with anti-*Lachesis* serum (900%) (Table 3).

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Table 1. Distribution of the total number of cases and the proportion of clinical complications in accidents by venomous animals in Brazil between 2007 and 2019 according to sociodemographic and clinical, epidemiological aspects. Brazil, 2022.

	Total cases (%)[a]	Complicated cases (%)[a]	Proportion of clinical complications (per 1,000 cases)
Gender			
Man	1,216,328 (56.2%)	25,602 (65.8%)	21.0
Woman	948,317 (43.8%)	13,332 (34.2%)	14.0
Total	2,164,645 (100%)	38,934 (100%)	-
Skin color			
White	792,628 (42.7%)	16,163 (44.7%)	20.3
Black	118,660 (6.4%)	2,218 (6.1%)	18.6
Asian	16,357 (0.9%)	326 (0.9%)	19.9
Mixed-race	906,137 (48.9%)	16,401 (45.4%)	18.0
Indigenous	20,828 (1.1%)	1,012 (2.8%)	48.5
Total	1,854,610 (100%)	36,120 (100%)	-
Educational attainment			
Illiterate	49,579 (3.6%)	1,492 (5.4%)	30.0
Incomplete 1st to 4th grades	249,899 (18.2%)	6,439 (23.1%)	25.7
Complete 4th grade	127,514 (9.3%)	2,923 (10.5%)	22.9
Incomplete 5th to 7th grades	251,287 (18.3%)	5,227 (18.8%)	20.8
Complete elementary school	111,902 (8.2%)	2,116 (7.6%)	18.9
Incomplete Middle School	116,766 (8.5%)	2,010 (7.2%)	17.2
Complete Middle School	211,528 (15.4%)	3,141 (11.3%)	14.8
Incomplete higher education	23,656 (1.7%)	412 (1.5%)	17.4
Complete Higher Education	42,144 (3.1%)	762 (2.7%)	18.0
Not applicable	186,185 (13.6%)	3,331 (12%)	17.8
Total	1,370,460 (100%)	27,853 (100%)	-
Place of occurrence			
Urban	1,152,485 (55.8%)	13,635 (35.9%)	11.8
Rural	889,237 (43.0%)	23,714 (62.4%)	26.6
Periurban	23,993 (1.2%)	627 (1.7%)	26.1
Total	2,065,715 (100%)	37,976 (100%)	-
Time between accident and care			
0 – 1 hours	923,725 (43.8%)	7,359 (19.3%)	7.9
1 – 3 hours	520,389 (24.7%)	7,318 (19.2%)	14.0
3 – 6 hours	184,675 (8.8%)	4,317 (11.3%)	23.3
6 – 12 hours	85,990 (4.1%)	2,809 (7.4%)	32.6
12 – 24 hours	93,855 (4.4%)	3,636 (9.5%)	38.7
24 or more hours	146,986 (7.0%)	10,374 (27.2%)	70.5
Ignored	153,718 (7.3%)	2,306 (6.0%)	15.0
Total	2,109,338 (100%)	38,119 (100%)	-
Accident site			
Head	126,963 (6.1%)	1,736 (4.5%)	13.6
Arm	117,194 (5.7%)	1,905 (5.0%)	16.2
Forearm	65,638 (3.2%)	1,198 (3.1%)	18.2
Hand	342,096 (16.5%)	4,624 (12.1%)	13.5
Finger	339,605 (16.4%)	3,468 (9.1%)	10.2
Torso	110,528 (5.3%)	2,054 (5.4%)	18.5
Thigh	87,494 (4.2%)	2,710 (7.1%)	30.9
Leg	191,439 (9.3%)	7,195 (18.8%)	37.5
Foot	526,498 (25.4%)	11,222 (29.4%)	21.3
Toe	161,995 (7.8%)	2,109 (5.5%)	13.0
Total	2,069,450 (100%)	38,221 (100%)	-
Cause of accident			
Snakes	366,968 (17.4%)	16,197 (42.9%)	44.1
Spiders	366,510 (17.3%)	11,446 (30.3%)	31.2
Scorpions	1,082,607 (51.2%)	6,128 (16.2%)	5.6
Caterpillars	54,811 (2.6%)	488 (1.3%)	8.9

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Bees	155,868 (7.4%)	1,692 (4.5%)	10.8
Other	87,891 (4.2%)	1,840 (4.9%)	20.9
Total	2,114,655 (100%)	37,791 (100%)	-
Snake genus			
Bothrops	263,473 (81.3%)	12,466 (83.0%)	47.3
Crotalus	28,439 (8.8%)	1,441 (9.6%)	50.6
Lachesis	2,977 (0.9%)	89 (0.6%)	29.8
Elapidae	10,021 (3.1%)	887 (5.9%)	88.5
Other (Non-venomous)	19,015 (5.9%)	132 (0.9%)	6.9
Total	323,925 (100%)	15,015 (100%)	-
Case classification			
Mild	1,724,368 (83.6%)	11,839 (31.7%)	6.8
Moderate	297,334 (14.4%)	17,248 (46.2%)	58.0
Severe	41,669 (2.0%)	8,285 (22.2%)	198.8
Total	2,063,371 (100%)	37,372 (100%)	-
Serotherapy			
Yes	477,532 (23.4%)	21,867 (58.3%)	45.7
No	1,566,791 (76.6%)	15,614 (41.7%)	9.9
Total	2,044,323 (100%)	37,481 (100%)	-
Work-related accident			
Yes	286,061 (15.1%)	10,459 (28.8%)	3.6
No	1,605,809 (84.9%)	25,821 (71.2%)	1.6
Total	1,891,870 (100%)	36,280 (100%)	-
Case evolution			
Cure	1,986,941 (99.8%)	33,195 (95.4%)	1.6
Death	3,426 (0.2%)	1,435 (4.1%)	41.8
Death from other causes	408 (0.0%)	172 (0.5%)	42.1
Total	1,990,775 (100%)	34,802 (100%)	-

a: valid cases.
Source: Information System for Notifiable Diseases, 2022

Table 2. Temporal trend of the annual incidence of total and complicated cases. 2007 to 2019. Brazil, 2022.

Macroregion	Variable	PPV (%)	Model	Trend
North	AITC	55.78	$Y=8.949-0.030X+0.012X2+0.010X^3$	Increasing
			$R^2=0.907$	p<0.001
	AICC	-28.17	$Y=4.734-0.315X+0.009X2+0.005X^3$	Decreasing
			$R^2=0.902$	p<0.001
Northeast	AITC	-63.36	$Y=8.299-0.695X+0.063X^2$	Decreasing
			$R^2=0.942$	p<0.001
	AICC[a]	9.3	NA[b]	NA[b]
			NA[b]	NA[b]
South	AITC	16.81	$Y=9.566+0.154X+0.033X^2$	Increasing
			$R^2=0.703$	p<0.001
	AICC[a]	-14.89	NA[b]	NA[b]
			NA[b]	NA[b]
Southeast	AITC	-44.83	$Y=10.585-0.561X+0.035X^2$	Decreasing
			$R^2=0.875$	p<0.001
	AICC	67.21	$Y=0.712+0.035X+0.002X^2$	Increasing
			$R^2=0.768$	p<0.001
Midwest	AITC	-58.18	$Y=30.530-1.500X-0.120X^2$	Decreasing
			$R^2=0.682$	p<0.001
	AICC[a]	56.48	NA[b]	NA[b]
			NA[b]	NA[b]

Other comparisons showed no statistical significance.
b: not applicable.
PPV: percentage of proportional variation.
IACT: annual incidence of total cases.
AICC: annual incidence of total cases.
Source: Information System for Notifiable Diseases, 2022

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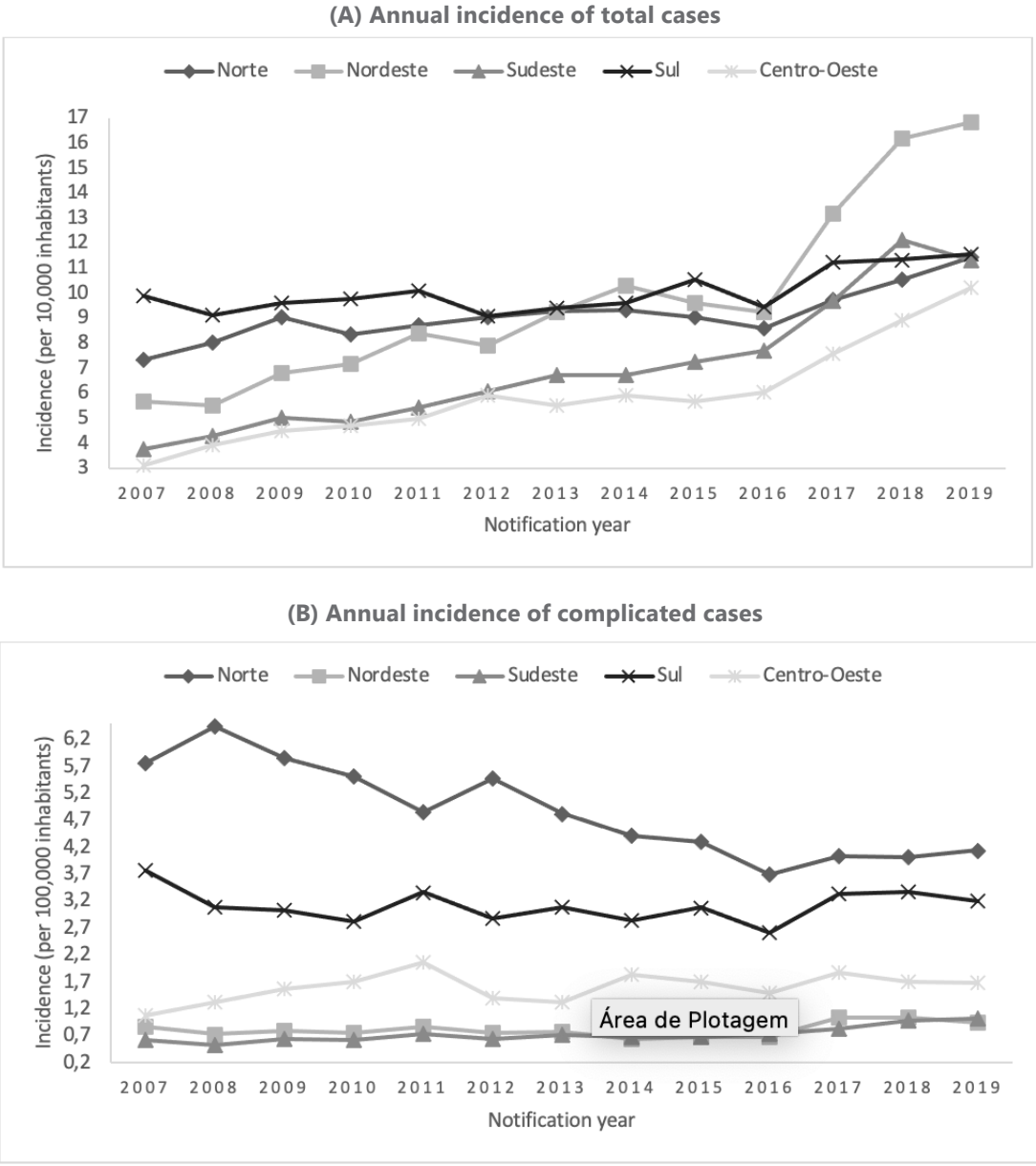

Figure 1. Annual incidence of total and complicated cases due to accidents by venomous animals in Brazil per region and notification year. Brasil 2022.
Source: Information System for Notifiable Diseases, 2022

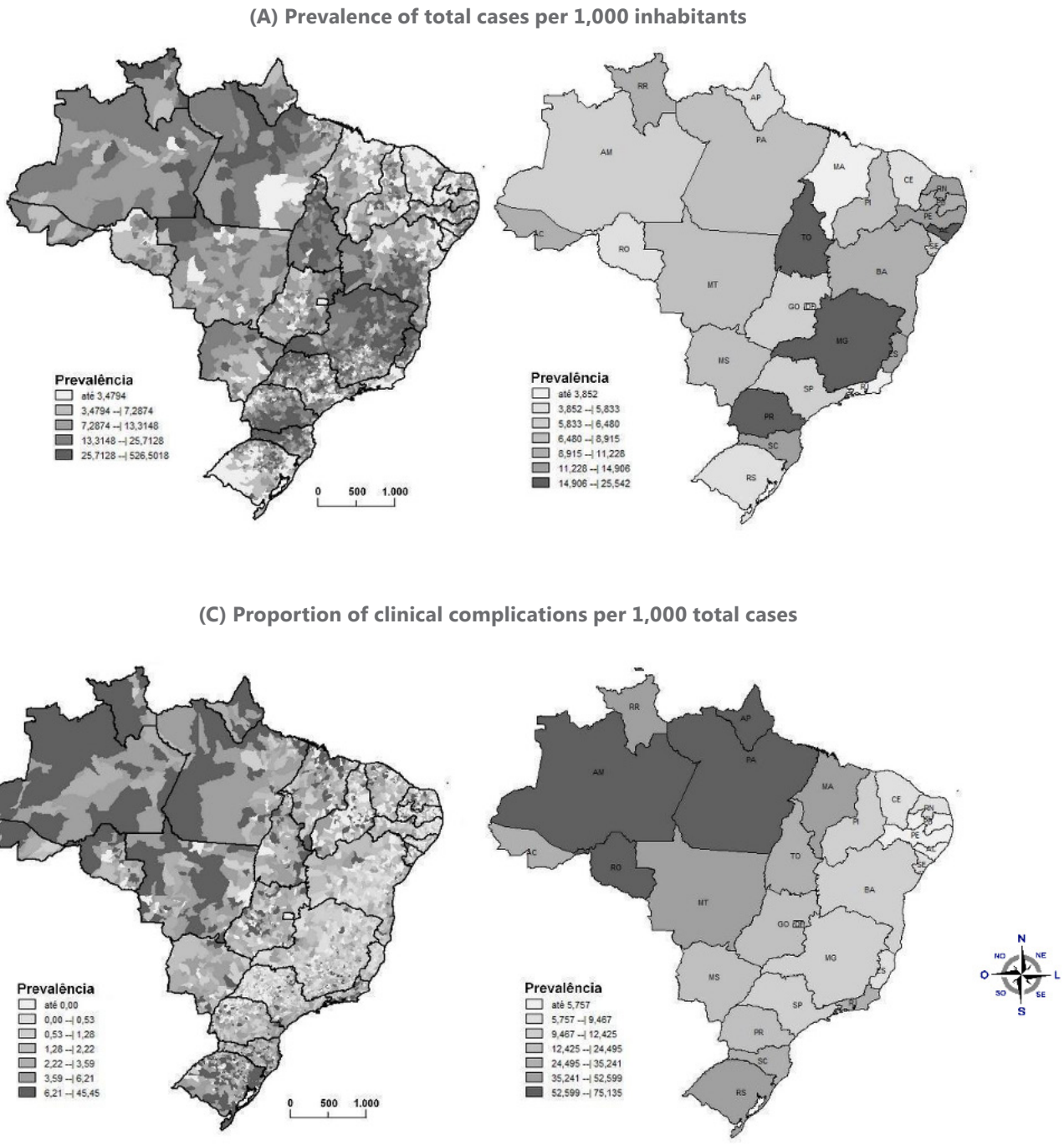

Figure 2. Spatialization of the prevalence of total and complicated cases and the proportion of clinical complications due to accidents by venomous animals in Brazil by municipality and federative unit. Brasil 2022.
Source: Information System for Notifiable Diseases, 2022

Table 3. Mean immunobiological ampoules used per patient due to clinical complications. Brazil, 2022.

Immunobiological agent	Average per patient without complications	Average per patient with complications	Percentage increase (%)
Anti-*Bothrops*	0.61	2.27	272
Anti-*Crotalus*	0.08	0.39	387
Anti-*Arachnid*	0.04	0.19	375
Anti-*Bothrops-Lachesis*	0.05	0.32	540
Anti-*Elapidae*	0.01	0.02	100
Anti-*Lachesis*	0.01	0.1	900
Anti-*Bothrops-Crotalus*	0.04	0.16	300
Anti-scorpion	0.16	0.4	150
Antilonomic	0.01	0.03	200

Source: Information System for Notifiable Diseases, 2022

DISCUSSION

Our epidemiological data showed a higher proportion of clinical complications due to accidents by venomous animals in Brazil among illiterates, Indigenous individuals, men, and rural inhabitants, findings which corroborate a study conducted in inner Minas Gerais in 2017, showing the predominance of cases involving economically active males, especially during agricultural activities and cattle production.[14] Thus, health actions and services aimed at ensuring sanitary equity must consider these populations' greater vulnerability.

Most studies evaluated the social and demographic profile of general cases of accidents by venomous animals, ignoring their clinical complications. A study conducted in northeastern Brazil found a prevalence of accidents involving scorpions, women, and mixed-race individuals.[15] Thus, victims of venomous animals differ from those who developed clinical complications due to them. Thus, healthcare management and professionals must pay especial attention to the differences among these populations.

In another perspective, a study conducted in inner Amazonas on ophidian accidents showed the greater expressiveness of clinical complications if inoculation occurred in victims' lower feet and legs, which agrees with the numbers in this study[16] However, research based on the medical records of children admitted to a hospital in the municipality of Montes Claros-MG discussed the greater prevalence of complicated cases due to scorpions inoculating victims' hands, arms, and forearms.[17] Thus, although the relation between inoculated anatomical areas and case complications suffers influence from the venomous animal and victims' characteristics, limbs configure the topographic regions most involved in clinical complications.

Clinical complications in upper and lower limbs are associated with victims' reduced income and greater public spending in social assistance, social security, and health as they can cause amputation and permanent limitation and/or disability, compromising individuals' autonomy and capacity for work, especially in family agriculture and manufacturing.[18]

Reducing the time between accidents and care administration is a fundamental measure to prevent case complications since estimates suggest that a lethality rate around 4.1% for care given 12 hours after accidents.[17, 19] This explains our findings as it shows that the proportion of clinical complications was almost nine times higher among users who received care 24 hours after the accident than among those who received care in the first hour, showing the need for a functioning and articulated health network and well implemented policies (especially the national Workers' s Health Policy), in which healthcare providers receive training to offer quick, effective, and direct care and monitor such injuries.

This study also found a higher proportion of clinical complications among Indigenous people. In areas far from reference health services, such as Indigenous communities and *quilombolas*, popular knowledge often becomes the only way to cope with diseases and injuries - configuring a legitimate and efficient informal health system. However, as formal health care practices lack complementarity, inappropriate conducts may worsen clinical cases and delay medical care administration. Thus, the lack of articulation between traditional and scientific knowledge marginalizes traditional groups and perpetuates the inappropriate use of tourniquets, herbs and other substances at injury sites, and the oral suction of the inoculated venom.[20]

Snakes stood out in our analysis of the proportion of clinical complications according to venomous animal, especially those of *Lachesis* genus, as they inflict greater harm to humans, causing nausea, vomiting, abdominal cramps, diarrhea, compartment syndrome, abscesses, necrosis, hypotension, and shock[16,21] even though studies conducted in the Amazon on the clinical repercussions and victims' factors show that *Bothrops* snakes cause about 80-90% of all ophidian accidents. We also observed the epidemiological relevance of accidents involving spiders and scorpions, which, although not the most prevalent regarding animal types, evolve significantly to clinical complications.

Please cite this article as: *Tomaz, V. R., Soares, M., & Bonfada, D. (2023). Epidemiologia das complicações clínicas de acidentes provocados por animais peçonhentos no Brasil. Revista De Epidemiologia E Controle De Infecção, 13(1). https://doi.org/10.17058/reci.v13i1.17696*

Thus, *T. serrulatus*, *T. bahiensis,* and *T. stigmurus* cause the most scorpion-related accidents in Brazil. The first is found in the states of Bahia, Minas Gerais, São Paulo, Espírito Santo, Paraná, Rio de Janeiro, and Goiás; the second, in the Brazilian South and Southeast, and the third, in the Northeast.[22] Most incidents cause severe local pain, edemas, salivation, among other symptoms, but may evolve to cardiogenic shock. [21]

In turn, the spiders of the genera *Loxosceles, Phoneutria,* and *Latrodectus* cause most complicated cases as they tend to evolve to acute renal failure, disseminated intravascular coagulation, sepsis, and occasionally death. Although *Loxosceles* species are not aggressive, they can cause accidents if compressed, usually affecting people at their homes since, by seeking shelter from light, they find refuge in clothing, paintings, furniture, bricks, and other places.[21]

Although AITC decreased in the Southeast, AICC increased in the region, especially considering the prevalence of total cases in the state of Minas Gerais. These findings describe the environmental, social, and economic aspects predisposing individuals to attacks (irregular occupations, hydrographic networks, vegetation, land use, metalworks, railways, etc.) — especially regarding scorpion-related accidents — and the distribution of fauna in Brazil, regarding which we stress those by *T. serrulatus* in this state.[19,23] Biological, social, and environmental determinants influence populations' health conditions, as per the AITC and IACC data of each region.

Thus, both North and South regions showed ascending AITCs and descending IACCs not only due to their growing agriculture and unbridled urbanization — which leads to a greater exposure to accidents by venomous animals (especially due to inadequate housing conditions) — but also to how seasonality relate with the increasing number of notifications of accidents by snakes and scorpions (but not spiders[24]) in May and June, suggesting their increase during rainy and hot periods.

The recent growth of primary health care and health surveillance has contributed to increasing the number of notifications as it has expanded access to low complexity care to the target audience and better supplied information systems, although underreporting and accessibility remain problematic, hindering the further development of knowledge on accidents by venomous animals and their repercussions.[25]

Thus, aiming to minimize health care expenses by assisting these occurrences, the Ministry of Health released the Information Note No. 74/2016 - CGPNI/DEVIT/SVS/MS in 2016, aiming to rationalize the distribution of immunobiologicals and restrict their supply to strategic points under adequate infrastructure and professional training dependent on health information systems, i.e., supported by epidemiological data. This strategy tends to qualify the infrastructure of health services to care for accidents due to venomous animals.[12]

We also found that 45.7 cases in every 1,000 that underwent serotherapy evolved to clinical complications and 41.8 complicated cases in every 1,000, to death. In view of this, we stress that clinical management and the early infusion of immunobiologicals reduces mortality and morbidity as users receiving immediate treatment have shorter hospitalizations and evolve to systemic complications in a milder proportion than those who received serotherapy later.[17]

This study found a higher proportion of clinical complications among illiterates, Indigenous people, men, and rural population, users whose accidents stemmed from snakes, and those who had received late medical-hospital care. We also observed a higher proportion of clinical complications in severe cases, those which required serotherapy, and deaths. The annual incidence of complicated cases increases in the Southeast, as well as the proportion of clinical complications in the states of Amazonas, Rondônia, Amapá, and Pará.

Despite the reasonable scientific support for analysis of the notifications of total cases. few studies have specifically investigated secondary clinical complications, thus offering scarce findings for comparison, which represents a limitation in this study. We also consider underreporting and inadequate notifications as a limitation as they restrict analysis due to their varying completeness, consistency, and quality. We recommend the development of analytical research capable of inferring the associations among the variables described in this study, such as the social and economic impact of late medical care to victims of accidents by venomous animals.

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AUTHORS' CONTRIBUTIONS

Valentina Ribeiro Tomaz contributed to data analysis, interpretation, and writing of the first and subsequent drafts of this article. **Marcelo Luiz Medeiros Soares** contributed to the conception of this article, data analysis and interpretation, and writing the first and subsequent versions of this article. **Diego Bonfada** contributed to the conception of this article, data analysis and interpretation, writing the first and subsequent versions of this article, critical review, and final approval. All authors approved the final manuscript for submission and take responsibility for the integrity and accuracy of their work.

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

Revista de Epidemiologia e Controle de Infecção

Hospital Santa Cruz

ORIGINAL ARTICLE

Correlation between physical activity practice and mortality from COVID-19: an ecological study

Correlação entre prática de atividade física e mortalidade por COVID-19: um estudo ecológico

Correlación entre la práctica de actividad física y la mortalidad por COVID-19: un estudio ecológico

https://doi.org/10.17058/reci.v13i1.17944

Received: *14/10/2022*
Accepted: *03/01/2023*
Available online: *06/03/2023*

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ABSTRACT

Background and objective: new population-level studies are needed to better assess the relationship between physical inactivity and mortality from COVID-19. The aim of the study was to evaluate the correlation between population prevalence of physical activity and standardized mortality rates by COVID-19 in Brazilian capital cities and the Federal District. **Methods**: this is an ecological study, whose analysis is secondary. The prevalence of physical inactivity, insufficient physical activity, and physical activity during free time was obtained from the Surveillance of Risk Factors and Protection for Chronic Diseases by Telephone Survey 2019 (VIGITEL), according to minutes spent on leisure, commuting, and household activities. The COVID-19 mortality data was obtained from the Influenza Epidemiological Surveillance Information System (SIVEP-Gripe), adding the accumulated deaths until December 31, 2020. The resident population was estimated from the Instituto Brasileiro de Geografia e Estatística (IBGE) for the year 2020. Pearson Correlation evaluated the correlation between the prevalence of different physical activity practices and the standardized mortality rate from COVID-19, in total, and according to age groups. **Results:** there was a significant positive correlation (r = 0.420; p = 0.029) between the overall prevalence of insufficient physical activity and the standardized COVID-19 mortality rate. No correlation was observed between the other prevalence of physical activity and the standardized mortality rate from COVID-19. **Conclusion:** there was a correlation between insufficient levels of physical activity and the standardized mortality rate from COVID-19 in people living in Brazilian capital cities.

Keywords: COVID-19; Mortality; Physical Exercise; Sedentary Behavior; Correlation of Data.

RESUMO

Justificativa e objetivo: novos estudos em nível populacional são necessários para avaliar a relação entre inatividade física e mortalidade por COVID-19. O objetivo deste estudo foi avaliar a correlação entre as prevalên-

Please cite this article as: *Oliveira , L. P. de ., Hughes , H. M. F. B. R. ., Carneiro , R. A. V. D. ., Silva , C. J. T. da ., Ronsoni , K. F. ., Cascaes, A. M. ., Hillesheim, D., & Hallal , A. L. de L. C. . (2023). Correlação entre prática de atividade física e mortalidade por COVID-19: um estudo ecológico. Revista De Epidemiologia E Controle De Infecção, 13(1). https://doi.org/10.17058/reci.v13i1.17944*

cias populacionais de prática de atividade física e as taxas padronizadas de mortalidade por COVID-19 nas cidades capitais brasileiras e no Distrito Federal. **Métodos**: trata-se de um estudo ecológico, cuja análise é secundária. As prevalências de inatividade física, atividade física insuficiente e atividade física no tempo livre foram obtidas do inquérito Vigilância de Fatores de Risco e Proteção para Doenças Crônicas por Inquérito Telefônico 2019 (VIGITEL). Os dados de mortalidade por COVID-19 foram obtidos do Sistema de Informação de Vigilância Epidemiológica da Gripe (SIVEP-Gripe), somando os óbitos acumulados até 31 de dezembro de 2020. A população residente foi estimada a partir do Instituto Brasileiro de Geografia e Estatística (IBGE) para o ano de 2020. A Correlação de Pearson avaliou a correlação entre a prevalência de diferentes práticas de atividade física e a taxa padronizada de mortalidade por COVID-19, no total e segundo faixas etárias. **Resultados:** houve correlação significativa positiva (r = 0,420; p = 0,029) entre a prevalência geral de atividade física insuficiente e a taxa padronizada de mortalidade por COVID-19. Não foi observada correlação entre as demais prevalências de prática de atividade física e taxa padronizada de mortalidade por COVID-19. **Conclusão:** houve correlação entre os níveis insuficientes de atividade física e a taxa padronizada de mortalidade por COVID-19 em pessoas que vivem nas cidades capitais brasileiras.

Palavras-chave: COVID-19; Mortalidade; Exercício Físico; Comportamento Sedentário; Correlação de Dados.

RESUMEN

Justificación y objetivo: nuevos estudios a nivel poblacional son necesarios para evaluar la relación entre la inactividad física y la mortalidad por COVID-19. Evaluar la correlación entre la prevalencia poblacional de actividad física y las tasas estandarizadas de mortalidad por COVID-19 en las capitales brasileñas y el Distrito Federal. **Métodos:** se trata de un estudio ecológico, cuyo análisis es secundario. Las prevalencias de sedentarismo, actividad física insuficiente y actividad física en el tiempo libre se obtuvieron de la Encuesta Telefónica de Vigilancia de Factores de Riesgo y Protección de Enfermedades Crónicas 2019 (VIGITEL). Los datos de mortalidad por COVID-19 se obtuvieron del Sistema de Información de Vigilancia Epidemiológica de Influenza (SIVEP-Gripe), sumando las muertes acumuladas hasta el 31 de diciembre de 2020. La población residente se estimó del Instituto Brasileiro de Geografia e Estatística (IBGE) para el año. 2020. Pearson Correlation evaluó la correlación entre la prevalencia de diferentes prácticas de actividad física y la tasa de mortalidad estandarizada por COVID-19, en total y según grupos de edad. **Resultados:** hubo una correlación positiva significativa (r = 0,420; p = 0,029) entre la prevalencia general de actividad física insuficiente y la tasa de mortalidad estandarizada por COVID-19. No se observó correlación entre la otra prevalencia de actividad física y la tasa de mortalidad estandarizada por COVID-19. **Conclusión:** hubo una correlación entre los niveles insuficientes de actividad física y la tasa de mortalidad estandarizada por COVID-19 en personas que viven en las capitales brasileñas.

Palabras clave: COVID-19; Mortalidad; Ejercicio Físico; Comportamiento Sedentario; Correlación de Datos.

INTRODUCTION

The first alert of a possible Public Health Emergency of International Concern (PHEIC) reporting the emergence of pneumonia of unknown cause in Wuhan, China, was released by the International Health Regulations (IHR, 2005) on December 31, 2019. Soon, researchers from the World Health Organization (WHO) gathered to identify the new infectious agent from the spread of cases to other Asian countries, until the outbreak was finally declared as PHEIC on January 30, 2020.[1]

After more than a year of its beginning, the pandemic epicenter moved from the Asian continent to the Americas region, which, in December 2021, had more than 96 million cases of the disease (37.01% of the world total) and 2.3 million deaths (45.06% of the world total). Looking at Latin America, Brazil stands out by ranking third in the global ranking of disease cases, with about 22 million cases, and second in the world ranking of deaths, with approximately 614,000 deaths.[2] The challenge that COVID-19 poses for the Brazilian territory is accentuated by regional differences, with an uneven distribution of mortality and infections by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) among states.[3,4] Such regional differences have already been discussed by another study, which found higher mortality from COVID-19 in the northern region of the country, when compared with the same variable in the southeast region. The authors related this difference in mortality to the greater number of comorbidities present in places with a lower level of socioeconomic development.[5]

Regarding comorbidities considered risk factors for death from COVID-19, until October 2021, the Centers for Disease Control and Prevention (CDC) highlighted arterial hypertension, cardiovascular diseases, diabetes, cancer, chronic kidney disease, chronic lung disease, advanced age, and obesity as aggravating factors and indicators of poor prognosis.[6] However, the search for new risk factors associated with SARS-CoV-2 infection remains active. The regular practice of physical activity is already being discussed in the medical literature as a protective factor against chronic non-communicable diseases such as breast cancer, colorectal cancer, type II

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diabetes mellitus, ischemic heart disease, coronary heart disease, and stroke.[7] Regarding SARS-CoV-2 infection, a US hospital observational study associated constant physical inactivity with severe COVID-19 development. Also, in terms of poor disease evolution, the authors equate physical inactivity with other comorbidities and risk factors identified by the CDC, with the exception of advanced age and previous organ transplantation.[8]

Although this study suggests physical inactivity as a possible risk factor for COVID-19 mortality, further population-level studies are required to better understand this relationship. This is the first study to analyze variables of physical inactivity and insufficient physical activity prevalence correlated with COVID-19 mortality at the population level in capital cities in Brazil. Additionally, age stratification analysis can be an important factor in guiding actions, potentially generating implications for clinical practice.

Thus, considering the scarcity of population-level studies on the topic of physical inactivity as a possible risk factor for death from COVID-19, the unequal distribution of mortality rates in Brazilian territory and the availability of population-level data on these different variables, the present study aimed to evaluate the correlation between population prevalence of physical activity and standardized mortality rates by COVID-19 in Brazilian capital cities and the Federal District.

METHODS

Study design and data source

This is an ecological study, whose units of analysis were the 26 Brazilian capitals and the Federal District (FD). To obtain information about the practice of physical activity, data from the national Surveillance of Risk and Protection Factors for Chronic Diseases Survey by Telephone (VIGITEL) of the year 2019 was used. Managed by the Ministry of Health of Brazil, VIGITEL has collected data since 2006 on non-communicable chronic diseases and associated factors in the population aged 18 years old and over, with the aim of knowing the health status of these people and guiding programs and actions that reduce the occurrence of chronic diseases.[9] Detailed information about the VIGITEL sampling and data collection process was previously described.[10] Furthermore, data on mortality from COVID-19 was obtained from the Severe Acute Respiratory Syndrome (SARS) database, made available by the Influenza Epidemiological Surveillance Information System (SIVEP-Gripe).[11] Deaths accumulated up to December 31, 2020 and with laboratory confirmation for COVID-19 in the same capital cities evaluated by VIGITEL were included. Data on the resident population of cities was obtained from the Instituto Brasileiro de Geografia e Estatística (IBGE), the Brazilian statistics bureau, in the year 2020.[12]

Death rate from COVID-19

First, the crude mortality rate for COVID-19 was calculated through the ratio of the number of deaths in each capital city divided by the estimated population of the same city, multiplied by 100,000 population. Then, the rates were standardized by age, using the direct method[13] (10-year age groups), using the estimated age structure of the Brazilian population in 2020 as a standard. It is worth noting that this rate reflects the general population, as no data was found regarding the estimated population for 2020 in each capital city that included the age division "≥ 18 years old" for the standardization calculation.

Practice of physical activity

The practice of physical activity was assessed through three variables related to the prevalence of physical inactivity, insufficient physical activity, and physical activity during free time, as defined in VIGITEL, according to minutes spent on leisure, commuting, and household activities. Individuals who did not practice any physical activity in their free time in the last three months and who did not perform intense physical efforts at work, did not go to work or course/school by walking or cycling, for a minimum of 20 minutes in a one-way journey and, moreover, did not participate in the heavy cleaning of their homes were considered physically inactive. Individuals whose sum of minutes spent on physical activities in their free time, commuting to work/school and occupational activity did not reach the equivalent of at least 150 minutes per week of moderate intensity activities (or at least 75 minutes per week of vigorous-intensity activity) were classified as having insufficient physical activity. Finally, individuals with free time physical activity were those who practiced at least 150 minutes a week of moderate--intensity physical activity or commuting to school/work, or at least 75 minutes a week of vigorous-intensity physical activity. All variables were stratified according to age categories (18 to 24; 25 to 39; 40 to 59; 60 to 79; 80 years or older).[10]

Data analysis

Data was stored in *Microsoft Excel spreadsheets* and later exported and analyzed using software Stata , version 14.0 (StataCorp LP, College Station, United States). For the description of continuous variables, data was expressed as means, with their respective minimum and maximum values and 95% confidence intervals (95% CI). Shapiro-Wilk test was used to test the normality of the data for COVID-19 standardized mortality rate variable, in which the null hypothesis is that the population has a normal distribution. The prevalence of variables related to the practice of physical activity were weighted to adjust the sociodemographic distribution of the VIGITEL sample to the distribution of the city's adult population projected for the year 2019.

To assess the degree of correlation between the standardized mortality rate from COVID-19 and the variables related to the prevalence of physical inactivity, insufficient physical activity and physical activity during free time, Pearson's Correlation analysis was used to obtain the Coefficient Correlation (r), total and stratified for each age group (18 to 24; 25 to 39; 40 to 59; 60 to 79; 80 years or older). The statistical significance value adopted in this study was $p < 0.05$.

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Ethical aspects

VIGITEL was approved by the Brazilian National Research Ethics Commission (CAAE: 65610017.1.0000.0008). The data used in this research is in the public domain and was analyzed in aggregate, without identifying the participants, without the need for approval of the Research Ethics Committee (CEP), according to resolution No. 510, of April 7, 2016, of the Brazilian National Council of Health (CNS).

RESULTS

The average standardized mortality rate from COVID-19 in Brazilian capitals and the FD was 125.1 deaths per 100,000 population. The lowest rate (51.6/100,000 population) was found in Florianópolis (SC) and the highest (246.6/100,000 population) was found in Porto Velho (RO) (Table 1).

Deaths from COVID-19 occurred predominantly in the age group 60 to 79 years old (48.4%), followed by the age groups ≥ 80 (28.7%) and 40 to 59 years old (18.8%). Among individuals aged less than or equal to 39 years old, 4.1% of the deaths occurred.

Regarding the total prevalence of physical activity (physical inactivity, insufficient physical activity, and physical activity in their free time), it was observed that, among adults, 41.1% practiced physical activities during their free time and 44.4% had insufficient practice. Individuals aged 60-79 and 80 years old or older had the highest prevalence of physical inactivity and insufficient physical activity, while the groups 18-24 and 25-39 years old had the highest prevalence of free-time physical activity (Table 2).

A significant positive correlation (r = 0.420; p = 0.029) was found between the prevalence of insufficient physical activity and the standardized mortality rate from COVID-19, in total. There was no significant correlation between the prevalence of physical inactivity and the standardized COVID-19 mortality rate (r = 0.293; p = 0.138) and between the prevalence of free-time physical activity and the standardized COVID-19 mortality rate (r = - 0.153; p = 0.445), in total (Figure 1).

Table 1. Estimated resident population in 2020, accumulated deaths, crude, and age-standardized COVID-19 mortality rates in the 26 capital cities and the Federal District. Brazil, 2020.

Capital cities	Population	Deaths*	Crude mortality rate+	Standardized mortality rate+, ++
Aracaju	664,908	898	135.1	147.3
Belém	1,499,641	2268	151.2	163.1
Belo Horizonte	2,521,564	2082	82.6	65.3
Boa vista	419,652	334	79.6	151.7
Campo Grande	906,092	1045	115.3	116.8
Cuiabá	617,848	646	104.6	122.1
Curitiba	1,948,626	2384	122.3	109.3
Florianópolis	508,826	310	60.9	51.6
Fortaleza	2,686,612	4267	158.8	174.3
Goiânia	1,536,097	1952	127.1	136.1
João Pessoa	817,511	1106	135.3	143.0
Macapá	512,902	284	55.4	101.0
Maceió	1,025,360	1192	116.3	136.5
Manaus	2,219,580	2962	133.4	221.1
Natal	890,480	1070	120.2	119.7
Palmas	306,296	199	65.0	126.0
Porto Alegre	1,488,252	1898	127.5	89.9
Porto Velho	539,354	763	141.5	246.6
Recife	1,653,461	3410	206.2	186.9
Rio Branco	413,418	491	118.8	188.1
Rio de Janeiro	6,747,815	10752	159.3	123.2
Salvador	2,886,698	2952	102.3	107.5
São Luís	1,108,975	1009	91.0	113.2
São Paulo	12,325,232	15553	126.2	112.1
Teresina	868,075	1168	134.6	168.6
Vitória	365,855	613	167.6	139.9
Distrito Federal	3,055,149	3930	128.6	160.9
Total capital cities	50,534,279	65,538	129.7	125.1

** Deaths registered until 12/31/20 with laboratory confirmation for the disease.*
+ Rates calculated per 100,000 population.
++ Rate standardized by the direct method and by age, by the estimated population of Brazil in 2020.

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Table 2. Average, minimum, and maximum prevalence of physical inactivity, insufficient physical activity, and free time in the 26 capital cities and the Federal District according to age groups. Brazil, 2019.

Variable*	Average Prevalence	95% CI	Minimum	Maximum
Physical inactivity				
18 to 24	12.8	11.3 – 14.4	6.6	24.5
25 to 39	11.3	10.0 – 12.5	7.3	21
40 to 59	10.9	10.1 – 11.7	7.4	14.8
60 to 79	24.1	22.5 – 25.8	15.8	31
80 or older	51.1	47.8 – 54.4	36.3	69.8
Total	14.0	13.2 – 14.8	10.2	17.4
Insufficient physical activity				
18 to 24	36.3	34.6 – 38.1	29.6	44.3
25 to 39	38.9	36.9 – 40.8	32	51.9
40 to 59	44.6	43.2 – 45.9	37.3	53.7
60 to 79	60.2	58.5 – 61.8	53	70
80 or older	80.5	78.4 – 82.6	67.8	90.3
Total	44.4	43.2 – 45.6	39	49.8
Physical activity during free time				
18 to 24	51.6	49.8 – 53.4	44.1	60.6
25 to 39	46.4	44.6 – 48.2	36.8	53.4
40 to 59	36.8	35.3 – 38.3	30.7	44.9
60 to 79	30.5	28.7 – 32.3	22.4	41.4
80 or older	16.7	14.5 – 18.9	6.4	30.6
Total	41.1	39.6 – 42.5	34.6	49.9

** Weighted prevalence to adjust the sociodemographic distribution of the Vigitel sample to the distribution of the adult population from each city projected for the year 2019.*

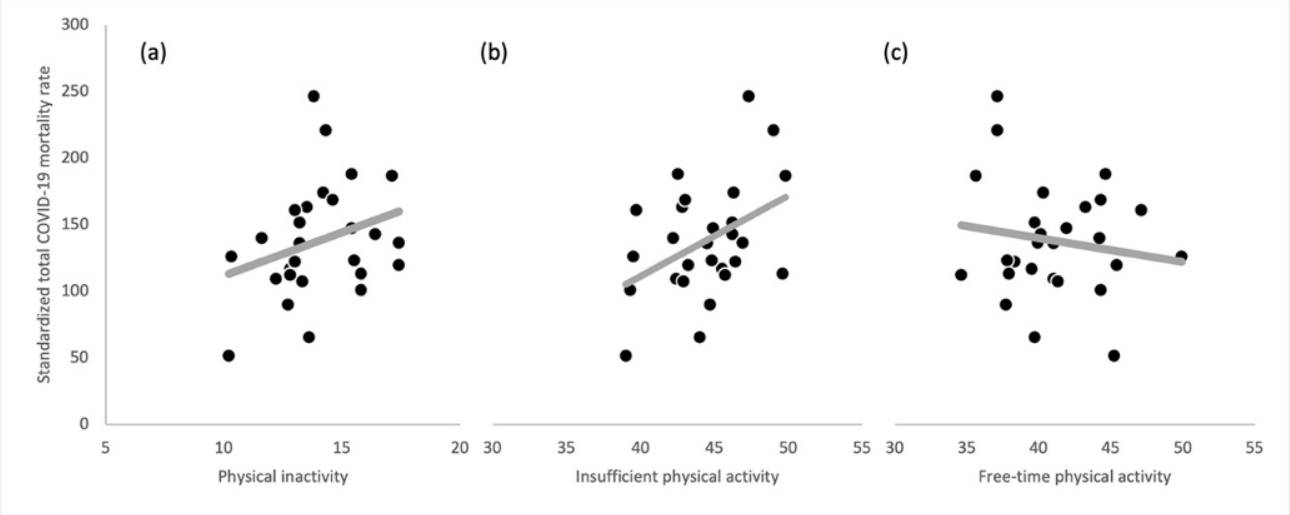

Figure 1. Correlation analysis between: (a) prevalence of total physical inactivity and standardized total COVID-19 mortality rate (r = 0.293; p = 0.138); (b) prevalence of total insufficient physical activity and standardized total COVID-19 mortality rate (r = 0.420; p = 0.029); (c) total free-time physical activity prevalence and total standardized COVID-19 mortality rate (r = -0.153; 0.445). Capital cities and the Federal District. Brazil. 2019-2020. r = *Pearson correlation coefficient.*

In the analysis stratified by age groups, a significant positive correlation was found between the prevalence of physical inactivity and the standardized rate of mortality from COVID-19 for groups aged 18 to 24 (r = 0.460; p = 0.015), 60 to 79 (r = 0.545; p = 0.003), and 80 years old or older (r = 0.648; p < 0.001). At the same time, a significant positive correlation was found between the prevalence of insufficient physical activity and the standardized COVID-19 mortality rate for groups aged 18 to 24 (r = 0.426; p = 0.026), 25 to 39 (r = 0.428; p = 0.025) and 40 to 59 years old (r = 0.404; p = 0.036). No significant result was found for the correlation between physical activity in free time and standardized mortality rate by COVID-19 in all age groups analyzed (Table 3).

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Table 3. Correlation analysis between the prevalence of different levels of physical activity and standardized COVID-19 mortality rates in capital cities and the Federal District. Brazil. 2019-2020.

Variable*	COVID-19 mortality rates	
	r*	P value
Physical inactivity		
18 to 24	0.460	0.015
25 to 39	0.061	0.760
40 to 59	0.162	0.418
60 to 79	0.545	0.003
80 or older	0.648	<0.001
Total	0.293	0.138
Insufficient physical activity		
18 to 24	0.426	0.026
25 to 39	0.428	0.025
40 to 59	0.404	0.036
60 to 79	0.369	0.057
80 or older	0.224	0.260
Total	0.420	0,029
Physical activity during free time		
18 to 24	-0.179	0.371
25 to 39	-0.230	0.247
40 to 59	-0.184	0.357
60 to 79	-0.281	0.155
80 or older	-0.262	0.186
Total	-0.153	0.445

** Pearson correlation.*

DISCUSSION

In the present study, all correlation coefficients were positive and significant in the physical inactivity category, with the exception of people aged 25 to 59 years old. In the case of the insufficient physical activity category, all the correlation coefficients obtained were positive, and only for people over 60 years old the value was not statistically significant. Still, analyzing the category of physical activity in free time, all correlation coefficients showed a negative correlation without statistical significance for all age groups. Finally, when the age groups were analyzed together, a significant result was noticed only for the prevalence of insufficient physical activity.

Since the declaration of PHEIC by the WHO,[1] lockdown and social distancing policies have been adopted by different authorities around the world. Such policies immediately resulted in necessary changes in habits and greater confinement of the population in their homes, which may have directly or indirectly limited the practice of physical activity in a diffuse way in these locations.[14] A survey review analyzed data from about 2 million participants in 168 countries, demonstrating that the prevalence of physical activity was low even before the pandemic, estimating approximately 1.4 billion people around the world at risk of exacerbation of diseases related to physical inactivity.[15] In Brazil, the effects of policies adopted to contain the pandemic, such as social distancing and quarantine, were also related to increased risk behaviors.[16]

Public policies to contain the pandemic in Brazil faced numerous challenges given the spread of fake news, misinformation, devaluation of vaccines, and promotion of disbelief in non-pharmacological actions as effective protective measures.[17-19] Still, there was no effective investigation through mass testing as in other countries because it was restricted only to individuals with severe symptoms, which may culminate in the difficulty of tracking viral spread.[20] Finally, there was little federal intervention in funding means to support the recovery of those infected,[19] when only about 23% of the Brazilian population has benefits through private health insurance plans.[21] The set of all these factors may be associated with a worse result of the country in facing the pandemic, reaching a greater number of cases and deaths.

The importance of physical activity in protecting against infections and systemic inflammation can be explained by several physiological processes. Among these effects, the following stand out: reduction in the amounts of molecules characteristic of the acute inflammatory phase, such as C-Reactive Protein (CRP) and interleukin-6 (IL-6); the maintenance and increase of muscle mass; [22] balance between the levels of anti-inflammatory (IL-4 and IL-1ra) and pro-inflammatory (IL-8, IL-1 and IL-1β) cytokines;[23] and increased recirculation of immune cells and greater efficacy of cytotoxic cells.[24] The regular practice of moderate physical activity is also associated with a lower number of infections of the upper respiratory tract[25,26] and a better response of the body to the application of vaccines, for example, against the Influenza virus.[27] Finally, there is evidence of a relationship between physical activity and changes in volume and muscle concentrations of the angiotensin-converting enzyme II (ACE II), [28] the main human binding receptor for the Spike antigen of the SARS-CoV-2 virus.[29] Thus, the documented role of physical activity in better immune functioning and in the maintenance of human physiology could help in the study at the population level.

The total analysis, without stratification by age groups, found a statistically significant result only for the prevalence of insufficient physical activity. This corroborates the results of national and hospital observational studies carried out in other countries, which associated the practice of physical inactivity with the development of severity by COVID-19 and reached the conclusion that there may be an increase in severity and mortality from COVID-19 according to previous levels of physical inactivity.[30-32] The results of these studies could encourage further investigation, as they present physical inactivity as a possible new risk factor for COVID-19.

When evaluating age stratification, not all correlations were statistically significant. However, the correlation patterns obtained in the analysis without age stratification were maintained: Negative correlation for physical activity during free time and positive correlation for insufficient physical activity and physical inactivity. Among the results highlights, there was a significance between the standardized mortality rate and the prevalence of physical inactivity for people aged over 60 years

old. This is worth noting, as advanced age is one of the main independent factors associated with mortality from COVID-19, since about 81% of deaths from the disease occurred in people over 65 years of age,[7,33] which determined the need for standardization to reduce this effect on correlation for this study. In addition, the age group between 18 and 24 years deserves mention for presenting significant results to positive correlations for the prevalence of physical inactivity and insufficient physical activity with the standardized mortality rate. A possible explanation for this finding is the fact that this population may have comorbidities. A person's risk of severe illness from COVID-19, and even death, increases as the number of underlying medical conditions they have increases, even in the young adult population.[6] In Brazil, Law Nº. 14,124, of March 10, 2021, pointed out that young people with comorbidity enter a priority group for vaccination against COVID-19.

This study has limitations due to the use of secondary data sources, as justified by the absence of correlation analysis in the age group below 18 years old, since VIGITEL restricts its physical activity prevalence sample to the population above or equal to 18 years old residing in Brazilian capitals and the Federal District. In addition, mortality rates from COVID-19 encompass the overall population, that is, it contains the population under 18 years old, however, it only represents 0.2% of the overall population.[11] Added to this, the exclusion of residents without landline telephones can cause a selection bias, since a predominance of certain prevalence for these individuals has already been evidenced: lower education levels, socioeconomic status, and access to health systems; and greater brown/black ethnicity, unemployment, and young age.[34] However, VIGITEL sought to apply post-stratification weight adjustments to better estimate survey prevalence and reduce the effect of this bias.[35] However it is important to note that data collection from self-reports may present underestimated or overestimated differences compared to measurements by movement tests, such as accelerometers and pedometers, and heart rate.[36,37] Regarding the questionnaire, VIGITEL does not use the Global Physical Activity Questionnaire (GPAQ) recommended by the WHO,[38] but a reproducible and already validated adaptation.[39] Furthermore, there was no agreement between the periods of the 2020 mortality data and the 2019 prevalence of physical activity, with the study being conducted before the highest peak of cases and deaths in Brazil, in the first semester of 2021.[40] Finally, the intrinsic limitations of an ecological study should be highlighted, such as dependence on the quality of secondary data and the ecological fallacy, since the latter makes it impossible to associate the practice of physical activity with mortality from the disease at an individual level.

In the present study, we observed a positive correlation between the overall prevalence of insufficient physical activity and the standardized mortality rate of COVID-19. Based on this finding, some implications for clinical practice can be cited, such as: recommending and encouraging regular physical activity for patients at increased risk of COVID-19, especially elderly individuals; identifying and addressing the lack of physical activity as a modifiable risk factor for worse outcomes in patients with COVID-19 and other chronic diseases; incorporating the evaluation of physical activity in the risk assessment for COVID-19 and considering physical activity as an integral part of the treatment and prevention plan for the disease; developing adapted and safe exercise programs for COVID-19 patients, including those hospitalized and in rehabilitation, to improve their functional capacity and reduce the risk of complications and mortality.

In addition, this result may encourage further in-depth studies to investigate the relationship between physical activity and COVID-19, including clinical trials to evaluate the effect of physical activity on the prevention and treatment of the disease.

The regular practice of physical activity is essential at any age and has been considered a means of preserving and improving human health and quality of life. By checking the correlation between the prevalence of physical activity practice and the standardized mortality rate from COVID-19 and examining people living in Brazilian capital cities, the total analysis showed a significant correlation when insufficient physical activity was studied. When analyzing the age groups, there was a significant correlation for groups from 18 to 24, 60 to 79, and 80 years old or older, for the prevalence of physical inactivity; and for groups 18 to 24, 25 to 39, and 40 to 59 years old, for the prevalence of insufficient physical activity.

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AUTHOR CONTRIBUTIONS

Lucas Paes de Oliveira: conceptualization, data curation; investigation; methodology; project administration; drafting, reviewing, and editing of the manuscript. **Helena Martinez Faria Bastos Régis Hughe, Raquel Alencastro Veiga Domingues Carneiro, Cleverton José Teixeira da Silva e Kamille Feltrin Ronsoni**: data curation; review and editing of the manuscript. **Danúbia Hillesheim**: formal analysis; methodology; review and editing of the manuscript. **Andreia Morales Cascaes e Ana Luiza de Lima Curi Hallal**: conceptualization; methodology; project administration; drafting, reviewing, and editing of the manuscript. All of the authors gave final approval of the version to be published and agreed to be accountable for all aspects of the study, ensuring that questions related to the accuracy or integrity of any of its parts have been appropriately investigated and resolved.