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Preparation, dissemination and information: *Epidemiology Center of Santa Cruz Hospital*
Fernando Abott Street, 174 - 2nd floor - Center - Santa Cruz do Sul/RS - CEP 96810-150
PHONE/FAX: 051 3713.7484 / 3713.7449 / E-MAIL: reci@hotmail.com
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Original Article

Association of Quick Sofa and Systemic Inflammatory Response Syndrome with mortality in septic patients

Associação do Quick Sofa e da Síndrome da Resposta Inflamatória Sistêmica com a mortalidade em pacientes sépticos

Asociación de Quick Sofa y Síndrome de Respuesta Inflamatoria Sistémica con mortalidad en pacientes sépticos

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Corresponding author:
E-mail: frighettovanessa@gmail.com
Address: Ramiro Barcelos Street, 2350, Porto Alegre, Rio Grande do Sul, Brazil.

Vanessa Frighetto Bonatto [1]
Jaqueline Sangiogo Haas[2]
Miriane Melo Silveira Moretti[1]
Arianne dos Santos Gomes[1]
Rafael Barberena Moraes[2]
Gilberto Friedman[1,2]
Karina de Oliveira Azzolin[1,2]

[1]Federal University of Rio Grande do Sul, Porto Alegre, Rio Grande do Sul, Brazil.
[2]Porto Alegre Clinical Hospital, Porto Alegre, Rio Grande do Sul, Brazil.

ABSTRACT

Background and Objectives: sepsis, a life-threatening condition, requires early identification. The Quick Sofa score may contribute to identifying the risk of sepsis in patients admitted to the emergency department. However, these scores and criteria need extensive testing before being implemented in clinical practice. This study aimed to evaluate the association between the Quick Sofa score and the Systemic Inflammatory Response Syndrome criteria with mortality in critically ill septic patients from a university hospital. **Methods:** a retrospective observational study including 614 patients aged over 18 years, admitted to the intensive care unit due to sepsis or septic shock. **Results:** no statistically significant differences were observed in the Quick Sofa or the Systemic Inflammatory Response Syndrome between survivors and non-survivors. Patients with a Quick Sofa score ≥2 were associated with the development of septic shock (p=0.00). Patients scoring ≥2 on Systemic Inflammatory Response Syndrome criteria showed a significant association with intensive care unit stays longer than 72 hours (p=0.013). **Conclusion:** the scores and criteria evaluated were not associated with mortality in septic patients. High mortality rates and the incidence of septic shock highlight the need for more effective tools for early diagnosis of sepsis.

Keywords: *Sepsis. Mortality. Organ Dysfunction Scores. Systemic Inflammatory Response Syndrome. Critical Care.*

RESUMO

Justificativa e Objetivos: a sepse, uma condição ameaçadora à vida, deve ser identificada precocemente. A escala QuickSofa pode contribuir para a identificação do risco de sepse em pacientes admitidos na emergência. No entanto, estes escores e critérios devem ser amplamente testados antes de serem inseridos na prática assistencial. O objetivo do estudo foi avaliar a associação entre o escore Quick Sofa e os critérios da Síndrome da Resposta Inflamatória Sistêmica com a mortalidade de pacientes sépticos críticos de um hospital universitário. **Método:** estudo observacional retrospectivo que incluiu 614 pacientes maiores de 18 anos, internados na unidade de terapia intensiva por sepse ou choque séptico. **Resultados:** não houve diferença estatisticamente significante entre as pontuações do escore Quick Sofa ou dos critérios da Síndrome da Resposta Inflamatória Sistêmica entre sobreviventes e não sobreviventes. Pacientes com escore Quick Sofa ≥2 apresentaram associação com o desenvolvimento de choque séptico (p=0,00). Pacientes com pontuação ≥2 nos critérios da Síndrome da Resposta Inflamatória Sistêmica tiveram associação estatisticamente significante com a permanência na unidade de terapia intensiva por mais de 72h (p=0,013). **Conclusão:** os escores e critérios avaliados não foram associados à mortalidade de pacientes sépticos. A alta mortalidade e a incidência de choque séptico reforçam a necessidade de ferramentas mais eficazes para o diagnóstico precoce da sepse.

Descritores: *Sepse. Mortalidade. Escores de Disfunção Orgânica. Síndrome da Resposta Inflamatória Sistêmica. Cuidado Intensivo.*

RESUMEN

Justificación y Objetivos: la sepsis, una condición que pone en riesgo la vida, requiere identificación temprana. La escala Quick Sofa puede contribuir a identificar el riesgo de sepsis en pacientes admitidos en el servicio de emergencias. Sin embargo, estos puntajes y criterios necesitan ser ampliamente evaluados antes de implementarse en la práctica clínica. Este estudio tuvo como objetivo evaluar la asociación entre el puntaje Quick Sofa y los criterios del Síndrome de Respuesta Inflamatoria Sistémica con la mortalidad en pacientes sépticos críticos de un hospital universitario. **Métodos:** estudio observacional retrospectivo que incluyó a 614 pacientes mayores de 18 años ingresados en la unidad de cuidados intensivos debido a sepsis o shock séptico. **Resultados:** no se observaron diferencias estadísticamente significativas entre las puntuaciones de Quick Sofa o Síndrome de Respuesta Inflamatoria Sistémica entre los sobrevivientes y los no sobrevivientes. Los pacientes con un puntaje Quick Sofa ≥2 presentaron asociación con el desarrollo de shock séptico (p=0,00). Los pacientes con una puntuación ≥2 en los criterios de Síndrome de Respuesta Inflamatoria Sistémica mostraron una asociación estadísticamente significativa con una estancia en la unidad de cuidados intensivos por más de 72 horas (p=0,013). **Conclusión:** los puntajes y criterios evaluados no se asociaron con la mortalidad en pacientes sépticos. Las altas tasas de mortalidad y la incidencia de shock séptico destacan la necesidad de herramientas más eficaces para el diagnóstico temprano de sepsis.

Palabras Clave: *Sepsis. Mortalidad. Puntuaciones en la Disfunción de Órganos. Síndrome de Respuesta Inflamatoria Sistémica. Cuidados Críticos.*

INTRODUCTION

Sepsis is a life-threatening condition, and its early identification and diagnostic criteria are challenging for health care professionals.[1] The Global Burden of Disease study has estimated 48.9 million cases of sepsis worldwide, with more than 11 million deaths, representing 19.7% of all global deaths, being considered a public health problem.[2,3]

In low- and middle-income countries, such as Brazil, the incidence and mortality by sepsis are considerably higher, ranging from 30 to 70%, however, epidemiologic data about sepsis are still scarce in those locations.[2,4] In Brazil, it is estimated that 30% of the Intensive Care Unit (ICU) beds are occupied by patients with sepsis or septic shock, and that the mortality surpasses 50%.[5]

In 2016, the Third International Consensus Sepsis-3 brought updated definitions of the disease, proposing that suspected infection together with organ dysfunction define the presence of sepsis.[1] The organ dysfunction, which was very dependent on the criteria of the Systemic Inflammatory Response Syndrome (SIRS), has been associated with the Sequential Organ Failure Assessment (SOFA) score in the ICU.[1] And for the identification of suspected cases of sepsis in the emergency departments and general hospital ward settings, where SIRS was also used, it was proposed the use of a score termed quickSOFA (qSOFA), a simplified form of SOFA for the identification of patients with a higher risk for sepsis.[1]

SIRS was devalued by the consensus Sepsis-3 as a screening tool because it is considered unspecific since it can precede organ dysfunction in conditions such as infection, trauma, pancreatitis and burns.[1] However, the qSOFA score, which was introduced in the same consensus, has been considered ineffective for the early identification of sepsis. Although qSOFA has high specificity, its sensitivity is low.[1] A meta-analysis showed a sensitivity of just 51.2% for the qSOFA criteria, while SIRS, despite less specific, has a superior sensitivity of 88,1%.[6] Thus, although qSOFA has increased the diagnostic specificity, it happened at the expense of a significant reduction in the sensitivity, which limits its efficacy for screening in populations of patients with less severity.[6]

In more resourceful settings, the consensus Sepsis-3 definitions have the potential to improve the identification of sepsis.[7] However, this is not the reality of developing countries with limited resources, such as Brazil, where the rapid identification of the disease is sought, prioritization of assistance to septic patients and the reduction in waiting times for admission to the ICU.[8] In these unfavorable scenarios, it is paramount that those scores and criteria are broadly validated before their insertion into the assistance routines.[8]

Even though low- and middle-income countries concentrate a significant proportion of the sepsis cases and deaths, the majority of the studies were carried out in high-income countries, where the resources and the epidemiologic characteristics differ substantially.[2] This disparity hinders the extrapolation of the findings due to the impact of the regional variations in prevalent pathogens, associated chronic diseases, and healthcare infrastructure.[9,10]

The applicability of qSOFA or SIRS in low- and middle-income countries, such as Brazil, is still not well researched, representing a significant gap in the knowledge.[8] This lack of data limits the development of effective diagnostic strategies, aligned with the local specificities. In limited resources settings, the early detection of sepsis should be the main focus of any initiative aiming to improve the quality and safety of assistance.[8,10]

In view of that, the objective of our study was to evaluate the association of the qSOFA score and the SIRS criteria with the mortality of critical septic patients in a university hospital in Brazil, adding to the assessment of these tools in a limited resources setting.

METHODS

Retrospective observational study carried out in a public, tertiary, university hospital located in Southern Brazil. It is an 860-bed hospital, from which 46 are for the emergency service and 60 are ICU. Patients aged 18 years or older, admitted to the ICU with a diagnosis of sepsis or septic shock were included in the study. Patients were followed up from the identification of organ dysfunction related to sepsis up until the hospital discharge or death. Data was collected from 2016 to 2017. Patients with incomplete records in the institution system were excluded from the study.

Information collected included sociodemographic data, comorbidities history, and clinical variables, such as the values of SAPS 3 (Simplified Acute Physiology Score 3). The outcomes analyzed were stay in the ICU over 72h, evolution to septic shock, and death. The organ dysfunction was identified in different wards such as general wards, emergency and ICU.

qSOFA score and SIRS criteria were evaluated from the signs and clinical symptoms recorded at the time of the first organ dysfunction related to sepsis. qSOFA allocates one point for each of the following clinical signs: systolic blood pressure <100 mmHg, respiratory rate > 22 rpm, and altered mental status (Glasgow Coma Scale≤ 14). On the other hand, SIRS criteria allocate one point to: temperature > 38.3ºC or < 36ºC, heart rate > 90 bpm, and respiratory rate > 20 rpm. Only the criteria possible to assess at the bedside were considered. Both scores were considered positive if ≥ 2.

This study included all eligible patients assisted from 2016 to 2017, with no previous sample calculation. This approach was taken to ensure the enrolment of as many patients as possible due to the retrospective nature of the study and the availability of data in the institution.

Statistical analyses were performed using the software Statistical Package for Social Sciences (SPSS), version 21.0. Categorical variables were described using absolute and relative frequencies, while continuous variables were presented as the mean and standard deviation, or the median and interquartile range (25–75), depending on the normality assessed by the Kolmogorov-Smirnov test. For the association analyses, the chi-squared test was used for categorical variables, Student's t test for the continuous variables with normal distribution, and Wilcoxon-Mann-Whitney for non-normal distributions. The discrimination performance was evaluated by the ROC curve (Receiver Operating Characteristic). The significance level was set at 5% ($p < 0.05$).

The study was conducted in accordance with the resolutions nº 466/2012, nº 510/2016, and nº 580/2018 from the Brazilian National Health Council, which regulate research involving human subjects. The project was approved by the institutional Research Ethics Committee under the number nº 16-0317, and by the Research Commission from the *Escola de Enfermagem da Universidade Federal do Rio Grande do Sul*. The project was inserted into Plataforma Brasil on August 17th, 2016, under CAAE 57326316300005327.

RESULTS

Six-hundred and fourteen patients diagnosed with sepsis were included in the study. They were predominantly young, with a high disease severity profile. The main infectious sites were the respiratory tract and abdomen. More than half of the patients had a community-acquired infection (Table 1).

Table 1. Sample characterization: sociodemographic aspects, clinical variables at the time of the diagnosis of sepsis, and times assessed. Data presented as mean and standard deviation, or median and interquartile interval (P25-P75), and absolute numbers and frequency, Porto Alegre, Rio Grande do Sul, 2016-2017.

Variables	
Age (years) mean±SD	60.7 ±15.5
Female n (%)	279 (45.4)
SAPS 3 mean±SD	67.8 ±14
Comorbidities n (%)	
Arterial Hypertension	297 (48.4)
Diabetes Mellitus	179 (29.2)
Neoplasia	133 (21.7)
Heart failure	116 (18.9)
Main infectious site n (%)	
Respiratory	314 (51.1)
Abdominal	131 (21.3)
Urinary	60 (9.8)
Others	109 (17.8)
Type of Infection n (%)	
Community-acquired	371 (60.4)
Ward of origin (organ dysfunction) n (%)	
Emergency	304 (49.5)
ICU	75 (12.2)
General wards	235 (38.2)
Time (days or minutes) Median (IQR)	
Total ICU stay	7.6 (3.8-14.0)
Total length of hospital stay	24.2 (12.9-43.0)
Length of time for the identification of sepsis (min)	30 (0-360.4)
Time interval between sepsis diagnosis and death	10.9 (5.1-23.0)

Abbreviations: Abbreviations: min= minutes; SD= standard deviation; N= absolute number; IQR= interquartile range.

Approximately 70% of the patients need mechanical ventilation in the first 24 hours after the diagnosis, and 27.2% needed infusion of vasopressor drugs. In the qSOFA score, the most frequent alteration was the respiratory, yet by SIRS criteria, heart rate alterations were more common.

Sepsis evaluation criteria and severity of disease were assessed in this sample (Table 2). An ICU stay longer than 72h occurred for 483 (78.7%) patients, and 283 (46%) presented septic shock. General mortality was 46.6% (286 patients), from which 48.8% (n=138) was in patients with septic shock.

Table 2. Scores and severity of septic patients admitted to the ICU of a public university hospital, Porto Alegre, Rio Grande do Sul, 2016-2017.

qSOFA score	
Median total (IQR)	1.0 (1-2)
Type of alteration n (%)	
Respiratory	326 (53.1)
Blood pressure	246 (40.1)
Neurologic	210 (34.2)
SIRS Criteria	
Type of Alteration n (%)	
Axillary temperature	252 (41)
Heart rate	432 (70.4)
Respiratory rate	361 (59)
Outcome n (%)	
Need ICU >72h	483 (78.7)
Septic shock	283 (46)
Death	286 (46.6)

Abbreviations: SD= standard deviation; n= Absolute number; IQR= interquartile range.

qSOFA score and SIRS criteria discrimination for mortality is represented by the ROC curve (Figure 1).

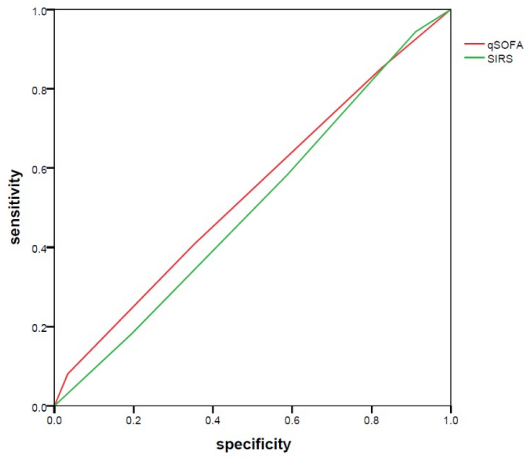

Figure 1. qSOFA score and SIRS criteria ROC curve for mortality.
qSOFA score (AUC ROC = 0.53, CI95%= 0.49-0.58, p-value= 0.09). SIRS criteria (AUC ROC= 0.50, CI95% 0.45-0.54, p-value = 0.96).

From 614 patients evaluated, 328 (53.4%) survived. When we compared the points for qSOFA score and SIRS criteria of the survivors and non-survivors, there was no statistically significant difference (Figure 2).

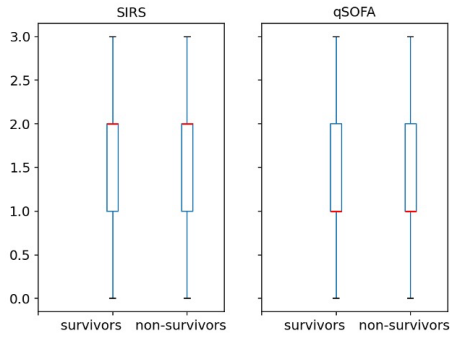

Figure 2. Evaluation of qSOFA ans SIRS scores between survivors and non-survivors.
Score Box-Plot, survivors/non-survivors: median qSOFA; (IQR): survivors 1.0 (1-2); non-survivors 1.00 (1-2); p-value* 0.073. Median SIRS;(IQR): survivors 2.0 (1-2); non-survivors 2 (1-2); p-value* 0.958. * Mann-Whitney test used to calculate significance.

qSOFA score and SIRS criteria, according to Sepsis-3 guidelines, were analyzed and presented to evaluate the association of the scores with survivors and non-survivors (Table 3).

Table 3. Association of qSOFA score and SIRS criteria with survivors and non-survivors.

Scores vs Non-survivors		Survivors	Non-survivors	Total	P-value*
qSOFA	< 2 n (%)	212 (55.6)	169 (44.4)	381 (100)	0.184
	≥ 2 n (%)	116 (49.8)	117 (50.2)	233 (100)	
SIRS	< 2 n (%)	135 (53.1)	119 (46.9)	254 (100)	0.975
	≥ 2 n (%)	193 (53.6)	167 (46.4)	360 (100)	

Evaluation of the association between qSOFA and SRIS ≥2 vs <2 points with the outcome non-survivor. P-value*= chi-squared test used to calculate significance. The percentage of each outcome is presented under the total number.

Patients with qSOFA ≥2 points presented association with the development of septic shock (p=0.00), but not with length of stay in the ICU (p=0.647). On the other hand, patients who had ≥2 points in SIRS criteria needed to stay for over 72h in the ICU (p=0.013), but there was no association with the development of septic shock (p=0.681) when compared with those patients with <2 points.

DISCUSSION

The findings of the present study revealed that there was no association between qSOFA and SIRS criteria with the mortality of critical septic patients. Likewise, there was no statistically significant difference in the mortality of patients with qSOFA score or SIRS criteria <2 e ≥2 points. However, SIRS ≥2 was associated with a longer ICU stay (p=0.013), while qSOFA ≥2 was associated with the development of septic shock (p=0.00). These results are in accordance with previous studies which pointed out the limitations of both scores in the prediction of mortality in severe septic patients.[11,12]

Multicentric studies, such as the ones conducted in Australia and New Zealand, had already showed those limitations.[11] Besides that, a systematic review revealed that qSOFA score has a high specificity (0.75), but a low sensitivity (0.41). On the other hand, SIRS criteria have a higher sensitivity (0.87), but the specificity is reduced. Such characteristics indicate that qSOFA is more effective to identify patients with higher risk of mortality, while SIRS can be more useful as a tool for an initial screening.[12]

Our study reinforces that, although both the score and criteria have limited clinical usefulness in the identification of septic patients with a high risk of death (AUC ROC <0.55), the sole use of qSOFA as a criterium for the early identification can delay even more the diagnosis in those patients.

In our findings, about 60% of the patients presented ≥2 points in SIRS, while only 38% scored ≥2 points in qSOFA, highlighting qSOFA's limitation for the early identification of sepsis cases in this population. Although qSOFA is useful to predict outcomes such as death and organic dysfunction in some locations, its low sensitivity reduces its effectiveness as a bedside screening tool.[13] Alternatives such as score qSOFA ≥1 or the addition of lactate in the evaluation have been suggested to improve the sensitivity in resource-limited settings.[14,15]

In low- and middle-income countries such as Brazil, where the access to ICU beds is limited and the demand for assistance is high, the early identification of sepsis is crucial, especially due to its high lethality.[16] Studies show that, in high-income countries, sepsis mortality ranges from 17 to 26%.[4] However, in Brazil, those rates are significantly higher, being as high as 41.6% in public hospitals.[17]

In our sample, mortality was 46.6% (n=286), being even higher among the patients with septic shock (48.8%, n=138). These numbers strongly contrast with the high-income countries and reinforce the obstacles encountered in Brazil, such as diagnostic delays and in the transfer to the ICU, which ideally should happen in up to six hours after the identification of sepsis.[4,16] They compromise the identification and the timely management of patients with a higher risk of death.[17]

Another relevant finding of the study is the ward of origin of patients at the time of organic dysfunction identification. Nearly half of the patients were diagnosed in the emergency department, which reinforces the need for screening tools that allow the early identification at the bedside. Currently, these patients get to the ICU in critical condition, with a mean SAPS 3 of 67.8±14 for survivors, and 71.7±14.3 for non-survivors, demonstrating high severity and mortality risk at the time of diagnosis.

Literature suggests that physiological alterations precede sepsis formal diagnosis in up to 8 hours and that the patient's survival depends on the team's ability to identify those alterations early and act quickly.[18,19] In this context, the role of the multidisciplinary team is crucial in the early identification of clinical deterioration signs and in the implementation of effective interventions.[20]

The 2021 Surviving Sepsis Campaign (SSC) recommends avoiding the sole use of qSOFA as a screening tool for sepsis or septic shock, giving preference to scores such as NEWS (National Early Warning Score) or MEWS (Modified Early Warning Score), which presented higher accuracy in different scenarios.[21] Nevertheless, qSOFA as well as SIRS are still widely used, and their validation in low- and middle-income countries is yet a hiatus that requires further studies.[21]

The study limitations are related to the data collection, which was done retrospectively. Another limitation is related to the patient's severity, since 88% of patients needed to be transferred to the ICU after the diagnosis of sepsis, which occurred initially at the general wards or emergency department. Future research about how to improve these models and increase the standardization of clinical protocols are paramount to make progress in the treatment of sepsis and its complications.

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AUTHORS' CONTRIBUTIONS

Vanessa Frighetto Bonatto contributed to the literature review, writing of the abstract, introduction, methods, discussion, results interpretation and description, tables elaboration, conclusions, review and statistical analysis. **Karina de Oliveira Azzolin** contributed to the writing of the abstract, methods, results interpretation, conclusions, review and statistical analysis. **Jaqueline Sangiogo Haas** contributed to the project management, literature review, writing of the abstract, introduction, methods, discussion, results interpretation and description, conclusions, review and statistical analysis. **Miriane Melo Silveira Moretti** contributed to the project management, literature review, writing of the abstract, introduction, methods, discussion, results interpretation and description, conclusions, review and statistical analysis. **Arianne dos Santos Gomes** contributed to the writing of the abstract, article review and submission. **Rafael Barberena Moraes** contributed to the writing of the abstract, methods, results interpretation, conclusions, review and statistical analysis. **Gilberto Friedman** contributed to the writing of the abstract, methods, results interpretation, conclusions, review and statistical analysis.

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

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Original Article

Outpatient follow-up of people living with HIV-1/Aids in the state of Piauí in the context of the Covid-19 pandemic

Acompanhamento ambulatorial de pessoas vivendo com HIV-1/Aids no estado do Piauí no contexto da pandemia de Covid-19

Seguimiento ambulatorio de personas que viven con el VIH-1/Sida en el estado de Piauí en el contexto de la pandemia de Covid-19

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Corresponding author:
E-mail: abichacra@ufpi.edu.br
Address: Federal University of Piauí, Department of Parasitology and Microbiology - SG 16. Ministro Petrônio Portella Campus, Ininga District, Teresina, Piauí, Brazil.

Francisco Rafael de Carvalho[1]
Wellinton Costa Araújo[2]
Lucas Dario Ferreira Santos[1]
Érika de Araújo Abi-chacra[1]

[1]Federal University of Piauí, Teresina, Piauí, Brazil.
[2]Teresina Technological Education Center, Teresina, Piauí, Brazil.

ABSTRACT

Background and Objectives: The Covid-19 pandemic has posed significant challenges to public health, especially for vulnerable groups such as people living with HIV-1/Aids (PLWHA). This study aimed to analyze the impact of the pandemic on sociodemographic aspects, clinical outcomes and opportunistic infections of PLWHA in outpatient care in Piauí. **Methods:** An observational epidemiologic study was conducted using retrospective data from medical records of PLWHA receiving outpatient care at the Natan Portella Institute of Tropical Diseases (IDTNP) in Teresina, Piauí. The sample consisted of 334 medical records of patients receiving antiretroviral therapy for at least six months. **Results:** Antiretroviral therapy (ART) showed significant efficacy before the pandemic, with a decrease in viral load between follow-up visits. During the pandemic, patients showed a decrease in viral load between follow-up visits, but the lack of complete data prevented a comprehensive analysis. CD4+ T-cell counts increased both before and during the pandemic, reflecting ART adherence. There was no significant difference in CD8+ T cell counts. The CD4+/CD8+ T cell ratio showed significant differences, indicating immunologic improvement. The most common opportunistic infections were syphilis, tuberculosis and neurotoxoplasmosis. **Conclusion:** The Covid-19 pandemic had a negative impact on ART adherence and increased the prevalence of co-infections among PLWHA in Piauí. Adaptive strategies, such as multi-month ART dispensing and the use of telemedicine, were crucial to ensure treatment continuity. This study highlights the need for adaptive public policies to ensure continuity of patient care during public health crises.

Keywords: *HIV-1. Covid-19. Health profile.*

RESUMO

Justificativa e Objetivos: A pandemia de Covid-19 tem representado desafios significativos para a saúde pública, especialmente para grupos vulneráveis como as pessoas vivendo com HIV-1/Aids (PVHA). Este estudo teve como objetivo analisar o impacto da pandemia nos aspectos sociodemográficos, desfechos clínicos e infecções oportunistas de PVHA em atendimento ambulatorial no Piauí. **Métodos:** Foi realizado um estudo epidemiológico observacional com dados retrospectivos de prontuários de PVHA atendidas em ambulatório do Instituto de Doenças Tropicais Natan Portella (IDTNP) em Teresina, Piauí. A amostra foi composta por 334 prontuários de pacientes que receberam terapia antirretroviral por pelo menos seis meses. **Resultados:** A terapia antirretroviral (TARV) apresentou eficácia significativa antes da pandemia, com diminuição da carga viral entre as consultas de acompanhamento. Durante a pandemia, os doentes apresentaram uma diminuição da carga viral entre as visitas de acompanhamento, mas a falta de dados completos impediu uma análise exaustiva. As contagens de células T CD4+ aumentaram tanto antes como durante a pandemia, refletindo a adesão à TAR. Não se registou qualquer diferença significativa nas contagens de células T CD8+. A razão de células T CD4+/CD8+ apresentou diferenças significativas, indicando uma melhoria imunológica. As infecções oportunistas mais comuns foram a sífilis, a tuberculose e a neurotoxoplasmose. **Conclusões:** A pandemia de Covid-19 teve um impacto negativo na adesão ao TARV e aumentou a prevalência de co-infecções entre as PVHA no Piauí. Estratégias adaptativas, como a dispensação multi-mensal de TARV e o uso da telemedicina, foram cruciais para garantir a continuidade do tratamento. Este estudo destaca a necessidade de políticas públicas adaptativas para garantir a continuidade do atendimento aos pacientes durante crises de saúde pública.

Descritores: *HIV-1. Covid-19. Perfil de saúde.*

RESUMEN

Justificación y Objetivos: La pandemia del Covid-19 trajo desafíos importantes a la salud pública, especialmente a los grupos vulnerables, entre ellos, los que portadores de VIH-1/SIDA (PVVS). Este estudio tuvo como objetivo analizar el impacto de la pandemia en los aspectos sociodemográficos, resultados clínicos e infecciones oportunistas de PVVS en seguimiento ambulatorio en el estado de Piauí. **Métodos:** Se realizó un estudio epidemiológico observacional, en el que se utilizaron datos retrospectivos de historiales médicos de PVVS en tratamiento ambulatorio en el Instituto de Dolencias Tropicales Natan Portella (IDTNP), de Teresina, Piauí. La muestra estuvo constituida por 334 historias clínicas de pacientes bajo tratamiento antirretroviral de aproximadamente seis meses. **Resultados:** Antes de la pandemia, la terapia antirretroviral (TARV) mostró una eficacia significativa, con reducción de la carga viral entre las visitas de seguimiento. Durante la pandemia, la carga viral de los pacientes también disminuyó entre las visitas de seguimiento, pero la falta de datos minuciosos ha obstaculizado un análisis más exhaustivo. Los recuentos de células T CD4+ aumentaron antes y durante la pandemia, lo que refleja la adherencia al TARV. No hubo gran diferencia en los recuentos de células T CD8+. Sin embargo, la relación TCD4+/TCD8+ mostró diferencias significativas, apuntando hacia una mejoría inmunológica. Las infecciones oportunistas más prevalentes fueron la sífilis, la tuberculosis y la neurotoxoplasmosis. **Conclusión:** la pandemia del Covid-19 impactó negativamente en la adhesión al TARV y aumentó la prevalencia de coinfecciones en PVVS en Piauí. Las estrategias adaptativas, como la dispensación del TARV por varios meses y la telemedicina, fueron cruciales para garantizar la continuidad del tratamiento. Este estudio destaca la necesidad de políticas públicas adaptativas para asegurar la continuidad de la atención al paciente durante las crisis de salud pública.

Palabras Clave: *VIH-1. Covid-19. Perfil de salud.*

INTRODUCTION

Covid-19 (coronavirus disease-2019), a respiratory disease caused by the SARS-CoV-2 virus, emerged in December 2019 in the city of Wuhan, Hubei Province, China.[1] The first cases of the disease were associated with pneumonia of unknown origin. Due to its high transmissibility, the disease spread rapidly around the world, and on March 11, 2020, the World Health Organization (WHO) declared the new coronavirus a pandemic.[2] Covid-19 can manifest in a variety of ways, from asymptomatic cases to severe cases requiring intensive care, such as mechanical ventilation in intensive care units (ICUs). The most common symptoms are fever, cough, sore throat and dyspnea. Severe cases may progress to acute respiratory failure (ARI).[3,4]

The health crisis caused by Covid-19 has posed a significant global public health challenge, particularly in terms of high hospitalization rates, morbidity and mortality, and transmissibility. Specific population groups, such as the older adult, those with co-morbidities (systemic arterial hypertension and diabetes mellitus), those in vulnerable situations (incarceration or living in favelas/slums) and immunosuppressed individuals (undergoing cancer therapy or living with HIV-1/Aids), have been identified as more susceptible and therefore more likely to experience severe complications of the disease.[2,5]

In the scenario of people living with HIV/Aids (PLWHA), the Covid-19 pandemic has posed additional challenges to the clinical management of these conditions. Outpatient care for these people has become more complex due to restrictions on mobility and access to health services.[6] Adherence to antiretroviral therapy (ART) and regular monitoring of viral load and T-lymphocyte counts (CD4+ and CD8+) are critical for treatment efficacy and prevention of serious complications, including opportunistic infections.[3,5] PLWHA are particularly vulnerable to co-infection and opportunistic infections.

PLWHA are particularly vulnerable to co-infections and opportunistic infections due to the immunosuppression caused by HIV-1. During the pandemic, the possibility of co-infection with SARS-CoV-2 posed a significant challenge, as it not only exacerbated pre-existing health conditions, but also increased the need for rigorous clinical follow-up adapted to the new realities imposed by Covid-19.[2,5-7]

The pandemic has brought unprecedented challenges to the follow-up of PLWHA, highlighting the importance of studies that assess the impact of the pandemic on outpatient care practices. Understanding how clinical variables and the prevalence of opportunistic infections were affected during this period is crucial to identify deficiencies in the health system and develop more effective strategies for future health crises. By addressing the obstacles faced by PLWHA, it is possible to enrich the existing literature and provide a solid foundation for the continuous improvement of public health policies, ensuring a more resilient response tailored to the needs of these patients.[5-7]

In view of this scenario, this study aimed to analyze the impact of the Covid-19 pandemic on sociodemographic aspects, viral and immunological markers, and opportunistic infections in PLWHA under outpatient follow-up in Piauí.

METHODS

Type of study

An observational and analytical study of an epidemiologic nature was conducted using a mixed-methods approach. The study was based on retrospective data extracted from clinical records of PLWHA receiving outpatient care at the Natan Portella Institute of Tropical Diseases (IDTNP).

Study location

The study was conducted at the IDTNP Outpatient Clinic in Teresina, Piauí. This center is known for its excellence in the treatment and prevention of tropical and infectious diseases and serves patients from various regions, including neighboring states such as Maranhão.

Instrument and data collection

Microsoft Excel® 2010 was used for tabulation and preliminary analysis of the data. Data were collected between December 2022 and October 2023 through medical records and administrative records available at the Medical Archive and Statistics Service (MASS) of the IDTNP Outpatient Clinic.

Sample population

The sample consisted of 372 medical records of PLWHA receiving outpatient care at IDTNP. Before the pandemic, follow-up visits occurred at a normal interval (six months), but during the pandemic, visits usually occurred over a longer period.

Inclusion and exclusion criteria

Patients of both sexes, aged 18 years or older, with a confirmed diagnosis of HIV-1 and in outpatient treatment for at least six months were included. Medical records with incomplete data, patients who did not adhere to the established minimum treatment regimen, patients who died during the study period, and patients who did not receive outpatient follow-up during the pandemic were excluded.[8-11]

Study variables

The variables studied included: sociodemographic aspects (gender, age group, municipality of residence), viral markers (plasma HIV-1 viral load), immunologic

markers (quantification of lymphocytes TCD4+, TCD8+, and TCD4+/TCD8+ ratio), and record of opportunistic infections in PLWHA.[8-11]

Time frame

The study employed a detailed temporal analysis, defining the interval through December 2019 as the pre-pandemic period and January 2020 through January 2022 as the pandemic period.

Data analysis and interpretation

The sample consisted of 372 medical records for sociodemographics and opportunistic infections, and 334 medical records for viral and immunologic markers due to lack of follow-up during the pandemic. In the statistical analysis, the Wilcoxon test was used for paired data comparing the medians of viral load, MCT4+, CD8+, and MCT4+/MCT8+ ratio before and during the Covid-19 pandemic, with values of $p \leq 0.05$ considered significant. Bioestat 5.0 software (Instituto Mamirauá, Brazil) was used to generate the graphs. Descriptive analysis was applied to socio-demographic aspects and opportunistic infections, presented in tables with absolute and relative frequencies.

Ethical and legal aspects

This study was approved by the Research Ethics Committee of the Federal University of Piauí, under CAAE number 62729722.6.0000.5214, approval opinion No. 6.750.383 and approval date April 8, 2024.

RESULTS

Sociodemographic Variables of PLWHA from the IDTNP

Of the 372 patients, most are male, representing 70.2% of the sample, while females represent 29.8%. The distribution by age group shows that most patients are in the age group 40 to 49 years (30.1%), followed by the group 30 to 39 years (22.6%) and 50 to 59 years (22.0%). Patients aged 60 years and older represent 14.5% of the sample, while the lowest proportion is in the 18-29 age group (10.8%). Regarding the municipality of residence, most patients live in the capital city of Teresina (63.98%), while 31.72% come from other cities in the interior of Piauí and 4.30% from the state of Maranhão (Table 1).

Table 1. Distribution of absolute and relative frequencies of sociodemographic variables of PLWHA who undergo outpatient follow-up at IDTNP, Teresina – Piauí, 2024. (n=372)

Sociodemographic Variables	Absolute and relative frequency N (%)
Sex	
Male	261 (70.20)
Female	111 (29.80)
Age group	
18 to 29 years old	40 (10.80)
30 to 39 years old	84 (22.60)
40 to 49 years old	112 (30.10)
50 to 59 years old	82 (22.00)
60 years or older	54 (14.50)
Municipality of residence	
Capital	238 (63.98)
Other cities in the interior of Piauí	118 (31.72)
Maranhão	16 (4.30)

Viral markers - HIV-1 plasma viral load of PLWHA before and during the Covid-19 pandemic

At the first follow-up visit prior to the pandemic, patients had a high plasma HIV-1 viral load. However, starting at the second visit, a significant reduction in viral load was observed, as evidenced by the consistent decline in plasma HIV-1 RNA levels at subsequent visits. This progressive and significant decline, indicated by the statistical significance markers (**** and **), suggests that ART was effective in reducing viral load in patients followed prior to the pandemic (Figure 1A).

At the first follow-up visit during the pandemic, plasma HIV-1 RNA levels are similar to those observed before the pandemic, and patients have high viral loads. A significant decrease in viral load was observed during the pandemic, particularly between visits 1 and 2 (p=0.0008). However, a comprehensive comparison between all visits was not possible due to the lack of viral load data from patients at visits 3 and 4. Many data, such as plasma viral load and TCD4+ lymphocytes, were missing from some patients' medical records. Analyses were then performed using the data that was available from the patients. Therefore, in visits 2, 3, and 4 (during the pandemic), the number of patients in the analysis decreases because these data were not in the medical records and these tests were probably not performed during the pandemic. Despite the challenges posed by the pandemic, ART was effective in controlling patients' viral loads during this period (Figure 1B).

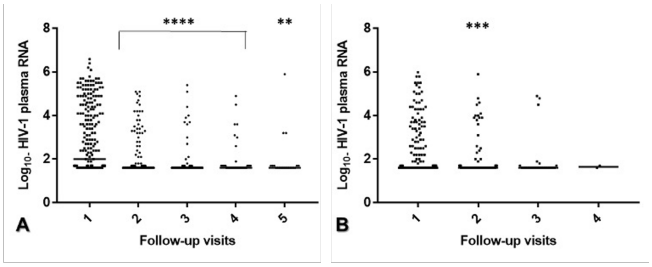

Figure 1. Plasma HIV-1 viral load of PLWHA before (A) and during (B) the Covid-19 pandemic at follow-up visits. (N=334). Horizontal lines represent median values and each

point represents a different patient at each visit. * p<0.05 - Wilcoxon U test.

Immunological markers – Quantification of TCD4+ and TCD8+ lymphocytes of PLWHA before and during the Covid-19 pandemic

During PLWHA follow-up visits, a gradual and significant increase in TCD4+ lymphocyte counts was observed prior to the pandemic (Figure 2A). At the first pre-pandemic visit, many patients were observed to have relatively low levels of TCD4+ cells. From the second visit, a significant increase in TCD4+ lymphocyte count was observed (1x2 visit: p<0.0001; 1x3 visit: p=0.0004; 1x4 visit: p=0.0002; 1x5 visit: p=0.0004). These results suggest a positive response to ART, which is also reflected in the decrease in viral load (Figure 1A).

During the pandemic, a significant increase in TCD4+ lymphocyte count was also observed between follow-up visits. Visit 1 compared to visit 2 resulted in a p=0.01 value, and visit 1 compared to visit 3 resulted in a p=0.04 value. However, it was not possible to make a complete comparison between all visits during the pandemic due to the lack of TCD4+ lymphocyte data from patients, especially at visit 4. This may be related to the difficulty in accessing health services and the suspension of several laboratory tests during the pandemic. However, it is noteworthy that the adherence of these patients to ART was reflected in the increase in TCD4+ cells observed in the present study (Figure 2B).

There was no significant difference in TCD8+ lymphocyte counts during the follow-up visits of the patients studied before the pandemic (Figure 2C) (1x2 visit: p=0.189; 1x3 visit: p=0.425; 1x4 visit: p=0.973; 1x5 visit: p=0.433). Similarly, no significant difference in TCD8+ cell counts was observed between follow-up visits during the pandemic (Figure 2D) (1x2 visit: p=0.84; 1x3 visit: p=0.85). However, a full comparison between all visits during the pandemic was not possible due to the lack of data on patients' TCD8+ cell counts, especially at visit 4. Similarly, the lack of data is closely related to the access of these patients to health services during this period and the suspension of many laboratory tests that should have been performed for the follow-up of PLWHA.

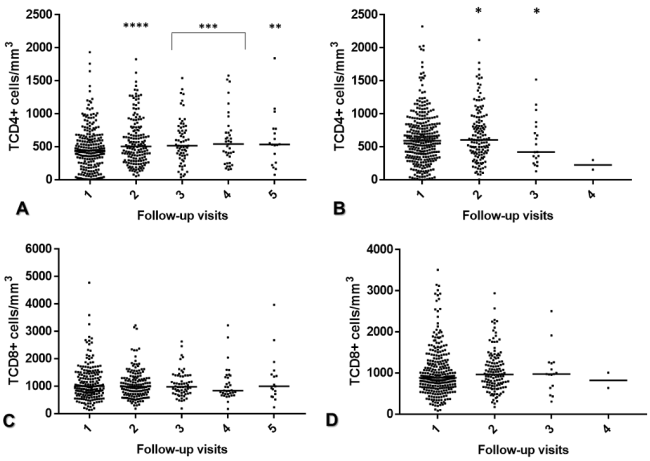

Figure 2. Absolute counts of TCD4+ lymphocytes (A and B) and TCD8+ lymphocytes (C and D) in PLWHA before (A and C) and during (B and D) the Covid-19 pandemic at follow-up visits. (n=334) Horizontal lines represent median values, and each point represents a different patient at each visit. * p<0.05 - Wilcoxon U test.

Immunological markers – Ratio of TCD4+/TCD8+ lymphocytes of PLWHA before and during the Covid-19 pandemic

A significant difference in the ratio of TCD4+/TCD8+ cells was observed at all follow-up visits before the pandemic (Figure 3A) (1x2 visit: p<0.0001; 1x3 visit: p<0.0001; 1x4 visit: p=0.0001; 1x5 visit: p=0.0006). These results showed a significant increase in the ratio of TCD4+/TCD8+ cells over the visits and a positive response to ART before the pandemic. During the pandemic, an increase in the ratio of TCD4+/TCD8+ cells between follow-up visits was also observed (Figure 3B) (1x2 visit: p=0.002; 1x3 visit: p=0.01). However, it was not possible to perform an analysis between all follow-up visits during the pandemic due to the lack of data on patients' TCD4+/TCD8+ lymphocyte counts, especially at visit 4. These results suggest that despite the difficulties posed by the pandemic, there was adherence to ART by PLWHA and significant immune recovery, as reflected by the increase in the ratio of TCD4+/TCD8+ lymphocytes.

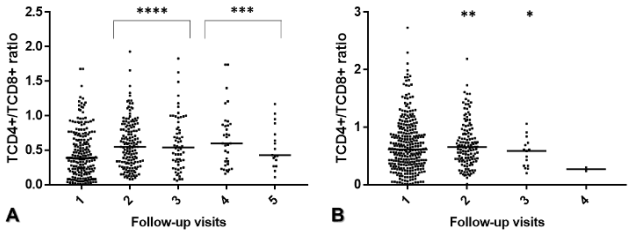

Figure 3. Number of TCD4+/TCD8+ lymphocytes in PLWHA before (A) and during (B) the Covid-19 pandemic at follow-up visits. (N=334). Horizontal lines represent median values and each point represents a different patient at each visit. * p<0.05 - Wilcoxon U test.

Opportunistic infections associated with PLWHA before and during the Covid-19 pandemic

Among the opportunistic infections recorded, syphilis, tuberculosis, and neurotoxoplasmosis were the most common, accounting for 17.2%, 8.3% and 6.2% of the total sample (n=372). Other opportunistic infections such as herpes zoster (1.9%), leishmaniasis (1.6%), hepatitis B (1.3%), and pneumonia (1.1%) presented significant values (Table 2). It is noteworthy that the "no record" category has the highest number and percentage, indicating that many cases have no documented opportunistic infection. This is probably related to the decrease in plasma HIV-1 viral load and the increase in TCD4+ lymphocytes (before and during the pandemic) observed in our study (Figure 1 and Figure 2).

Table 2. Distribution of absolute and relative frequencies of the main opportunistic infections presented by PLWHA undergoing outpatient treatment at IDTNP, Teresina – Piauí, 2024.

Opportunistic infections	Absolute and relative frequency (%)
No registration	223 (59.9)
Syphilis	64 (17.2)
Tuberculosis	31 (8.3)
Neurotoxoplasmosis	23 (6.2)
Herpes zoster	7 (1.9)
Leishmaniasis	6 (1.6)
Hepatitis B	5 (1.3)
Pneumonia	4 (1.1)
Moniliasis	2 (0.5)
Toxoplasmosis	2 (0.5)
Leprosy	2 (0.5)
Candidiasis	1 (0.3)
Meningitis	1 (0.3)
Cryptococcosis	1 (0.3)

DISCUSSION

The present study shows the predominance of men (70.2%) and the age group 40-49 years (30.1%) among the PLWHA followed up, confirming the findings of previous studies in Piauí.[8-11] This prevalence may be attributed to behavioral factors, such as risky sexual practices, and to the lower use of preventive health services by men. The predominant age group may reflect a longer history of infection prior to diagnosis, as suggested by studies indicating late diagnosis in adults in this age group.[8,9]

Most patients (63.98%) live in Teresina, the state capital, indicating better access to health services in the capital. This highlights the need to extend services to less supported regions, where a lack of infrastructure and resources can lead to delays in diagnosis and treatment.[8,10,11] Targeted strategies are needed to expand coverage and access to health services in peripheral and rural areas of the country. It is important to consider that the stigma associated with HIV-1 may lead people from rural areas to seek treatment in larger cities for greater anonymity.[8-11]

The present study shows a significant reduction in viral load after initiation of ART, confirming the findings of other studies demonstrating the efficacy of ART in suppressing HIV-1 viral replication.[12,14] This low viral load is essential as it indicates reduced viral replication, which significantly reduces the risk of disease progression and transmission of HIV-1. Patient adherence to ART is a critical factor in achieving these positive outcomes, underscoring the importance of health policies that encourage and support adherence.[13.15]

Despite the lack of data on some visits during the pandemic, the results suggest that patients adhered well to ART, that ART continued to be effective for most patients, and that many had access to treatment even during the pandemic. This is consistent with other studies indicating the relative resilience of PLWHA in maintaining regular use of ART.[16,17] The ability to keep viral load under control during a global health crisis underscores the importance of public health strategies that ensure treatment continuity even in adverse situations.[14.18]

Factors such as adherence to ART, the presence of comorbidities, and the severity of disease caused by HIV-1 are critical to understanding the trajectory of viral load during the pandemic.[16,19] Treatment adherence is particularly important to ensure continuity of viral suppression. In addition, continuous viral load monitoring is essential to assess the effectiveness of ART and to detect potential treatment failures, especially in times of crisis such as the Covid-19 pandemic.[20,21]

The gradual and significant increase in TCD4+ lymphocyte count after ART initiation is consistent with the existing literature.[13,14] Previous studies have shown that ART is highly effective in reconstituting the immune system, resulting in a substantial increase in TCD4+ lymphocyte count.[20,22] This immune recovery is critical, as it is associated with reduced susceptibility to opportunistic infections and significantly improves the quality of life of PLWHA. The increase in TCD4+ lymphocyte count prior to the pandemic underscores the effectiveness of ART in providing a robust immune recovery, which is critical in preventing complications associated with HIV-1.[21-23]

During the Covid-19 pandemic, increases in TCD4+ lymphocyte counts were observed, even with incomplete data at some visits, suggesting that ART maintained its efficacy in most patients and that PLWHA had good adherence to treatment. Studies suggest that continuity of antiretroviral treatment was essential to maintain the immune response, even in the face of the difficulties posed by the pandemic.[21,22] The importance of rigorous clinical follow-up of PLWHA, especially in times of crisis, is emphasized. Social distance and fear of Covid-19 infection made regular testing difficult, but adaptive strategies such as multi-month drug delivery and the use of telemedicine were essential to maintain treatment adherence and immune recovery in patients.[13,14,16,23]

However, regarding TCD8+ lymphocytes, this study found no significant difference in the number of these lymphocytes between the follow-up visits before and during the Covid-19 pandemic. However, they remained relatively stable, suggesting a consistent response to treatment even during the pandemic. This behavior is consistent with the literature indicating stability or minimal changes in TCD8+ lymphocyte counts in patients under effective treatment.[21,23] Although TCD8+ lymphocytes control the virus during acute HIV-1 infection, their cytotoxic potential declines dramatically as the disease progresses and they are no longer able to mount an adequate antiviral response. These lymphocytes undergo changes in their numbers, differentiation, and activation profile, and undergo immune exhaustion and progressive dysfunction.[19,21,23]

The ratio of TCD4+/TCD8+ lymphocytes is an important marker to assess immune recovery in PLWHA. In this study, a significant increase in the ratio of TCD4+/TCD8+ lymphocytes was observed at all follow-up visits, both before and during the pandemic. This increase is indicative of continued immune recovery and reflects the efficacy of ART in promoting recovery of TCD4+ lymphocytes and stabilization of TCD8+ lymphocytes. The literature highlights that an increasing ratio of TCD4+/TCD8+ lymphocytes is associated with a better immune response and a more favorable prognosis for PLWHA. The maintenance of this ratio during the pandemic suggests that despite the challenges posed by Covid-19, patients were able to maintain a robust immune response due to the continuity of antiretroviral treatment.[20-22]

The prevalence of opportunistic infections is a critical issue in the management of PLWHA. This study found a low incidence of opportunistic infections (40.1%) such as syphilis, tuberculosis and neurotoxoplasmosis among patients, which can be attributed to the efficacy of ART and sustained immune recovery. The significant reduction in viral load and increase in TCD4+ lymphocyte count play a critical role in preventing these infections, as a low viral load and increased TCD4+ lymphocyte count are indicators of a strengthened immune system that is less susceptible to opportunistic infections.[18,19,23,24]

During the Covid-19 pandemic, despite difficulties in maintaining regular follow-up, continuation of ART helped to maintain the immunological benefits and reduce the incidence of opportunistic infections. However, the pandemic may have affected the detection and registration of opportunistic infections due to limited access to health services.[22-25]

The Covid-19 pandemic posed significant challenges to the clinical follow-up of PLWHA, resulting in a reduction in face-to-face consultations and monitoring visits.[13] This posed a significant risk to the health of patients, compromising the continuous evaluation of treatment efficacy and the implementation of therapeutic adjustments when necessary. Studies carried out in Latin America, including Brazil and Venezuela, confirm these findings and demonstrate the negative impact of the pandemic on the follow-up of these consultations and examinations.[14-16]

In the face of this global health crisis, significant innovations in outpatient care were needed. At this point, adaptive interventions such as multi-month antiretroviral drug regimens in a single visit and telemedicine emerged as critical solutions. These strategies proved effective in maintaining treatment continuity and patient adherence.[13-16, 25]

In Piauí, at the IDTNP, the measure adopted during the pandemic to ensure treatment continuity and minimize patients' exposure to the risk of infection by the new coronavirus was to provide antiretroviral drugs for several months in a single visit. This approach is supported by the literature and has been shown to be an effective strategy for maintaining treatment continuity and patient adherence.[14.15]

The literature highlights the importance of telemedicine, which, although not used in the IDTNP context, is described as an essential solution in many contexts. Telemedicine enabled remote and continuous monitoring of patients, minimizing the need for face-to-face consultations and helping to prevent the spread of the SARS-CoV-2 virus.[16]

This study was also affected by the pandemic, resulting in incomplete data collection on viral and immunologic markers. This reduction has made it difficult to obtain accurate information on the health status of PLWHA, limiting the ability to conduct a comprehensive analysis of the impact of Covid-19 on this population.

In addition, the observational nature of the study prevents the inference of causality between variables, and it is necessary that future studies with experimental or quasi-experimental designs provide more robust evidence of cause and effect relationships.

This study, conducted on 372 PLWHA patients treated at the IDTNP in Teresina, Piauí, showed that most patients are male and that the predominant age group is between 40 and 49 years. Most patients reside in the capital city of Teresina, while a significant proportion come from other cities in the interior and the state of Maranhão.

In terms of viral markers, a significant reduction in HIV-1 plasma viral load was observed before and during the Covid-19 pandemic, despite interruptions in health care services. Immunologic markers, particularly TCD4+ lymphocyte counts, showed a significant increase both before and during the pandemic, indicating a positive response to antiretroviral treatment. However, TCD8+ lymphocyte counts remained relatively stable. The TCD4+/TCD8+ ratio also showed

a significant increase, suggesting continued immune recovery.

In terms of opportunistic infections, about 60% were unrecorded, of which syphilis, tuberculosis and neurotoxoplasmosis were the most common in the patients studied.

Although this study has made a valuable contribution to understanding the experience of PLWHA in Piauí during the Covid-19 pandemic, it is important to note some limitations. The sample of 372 PLWHA, although significant, may not be fully representative of the total population of PLWHA in Piauí, and the generalization of the results to other regions or socioeconomic contexts should be done with caution.

In short, the study highlights the importance of adaptive and innovative measures to ensure continuity of care for PLWHA, especially in times of public health crises such as the Covid-19 pandemic. The strategy implemented in IDTNP, the provision of antiretroviral drugs over several months, proved effective in maintaining treatment and the health of patients.

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AUTHORS' CONTRIBUTIONS

Francisco Rafael de Carvalho designed the project, analyzed and interpreted the data, and wrote the article. **Wellinton Costa Araújo** and **Lucas Dario Ferreira Santos** contributed to the relevant critical review of the intellectual content. **Érika de Araújo Abi-chacra** project design, analysis, interpretation of data and final approval of the version to be published.

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

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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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Original Article

Cases of Covid-19 among healthcare workers in the state of Bahia, 2020 to 2021

Casos de Covid-19 entre trabalhadoras(es) de saúde do estado da Bahia, 2020 a 2021
Casos de Covid-19 entre trabajadoras (es) de la salud en el estado de Bahía, 2020 a 2021

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Autor correspondente:
E-mail: sara_ssv@outlook.com
Endereço: Reitor Miguel Calmon Avenue, S/N - Vale do Canela, Salvador, Bahia, Brazil.

Sara de Santana Vieira[1]
Rafaella Santiago Coutinho Santos[1]
Milena Maria Cordeiro de Almeida[1]
Samilly Silva Miranda[1]
Handerson Silva Santos[1]
Luciano de Paula Moura[1]
Bruno Guimarães de Almeida[2]
Tatiane Araújo dos Santos[1]

[1]Federal University of Bahia, Salvador, Bahia, Brazil.
[2]Department of Management and Regulation of Health Work, Ministry of Health, Brasília, Brazil.

ABSTRACT

Background and Objectives: Health workers were among the main risk groups during the Covid-19 pandemic, thus understanding the profile of infected workers and monitoring exposure, of illness and the evolution of the disease in the workforce make it possible to recognize the determinants of different forms of risk and vulnerabilities related to the Covid-19 pandemic. This study aimed to describe the epidemiological profile of suspected cases of Covid-19 among healthcare workers in the state of Bahia. **Methods:** Epidemiological, cross-sectional and descriptive study, with health workers in the state of Bahia between May 2020 and December 2021. This is a census of workers, with data presented according to the results of Covid-19 tests: positive, negative or inconclusive. **Results:** Among the 45,173 tests, 24.7% had positive results and 0.3% inconclusive, with the majority of women (70.7%), aged 33-47 years old (46.9%), of technical educational level (45.0%), self-declared non-white (61.1%) and with an outsourced work contract (48.2%). No relevant differences appeared in the profile according to test results. **Conclusion:** The data reinforces the need to monitor and improve public strategies not only for detection, but also for the protection of health workers in the fight against the Covid-19 pandemic.

Keywords: *Covid-19. Workers Health Surveillance. Health Personnel. Workers Health. Epidemiology.*

RESUMO

Justificativa e Objetivos: Trabalhadoras(es) de saúde (TS) estiveram entre os principais grupos de risco durante a pandemia de Covid-19. Dessa forma, compreender o perfil das(os) trabalhadoras(es) infectadas(os) e realizar o monitoramento da exposição, do adoecimento e da evolução da doença na força de trabalho possibilitam o reconhecimento dos determinantes das diferentes formas de risco e vulnerabilidades relacionadas à pandemia de Covid-19. O objetivo deste estudo foi descrever o perfil epidemiológico dos casos suspeitos de Covid-19 entre TS do estado da Bahia. **Métodos:** Estudo epidemiológico, transversal e descritivo, com TS do estado da Bahia, entre maio de 2020 e dezembro de 2021. Trata-se de censo de TS, com dados apresentados segundo os resultados dos testes de Covid-19: positivo, negativo ou inconclusivo. **Resultados:** Dentre os 45.173 testes, 24,7% tiveram resultados positivos e 0,3% inconclusivos, com maioria de mulheres (70,7%), na faixa etária de 33-47 anos (46,9%), de escolaridade nível técnico (45,0%), autodeclaradas pardas (61,1%) e com vínculo de trabalho terceirizado (48,2%). Não apareceram diferenças relevantes no perfil, segundo resultados dos testes. **Conclusão:** Os dados reforçam a necessidade do monitoramento e aperfeiçoamento de estratégias públicas, não só de detecção, mas também de proteção às(aos) trabalhadoras(es) de saúde no combate à pandemia de Covid-19.

Descritores: *Covid-19. Vigilância em Saúde do Trabalhador. Pessoal de Saúde. Saúde do trabalhador. Epidemiologia.*

RESUMEN

Justificativa y Objetivos: Las (os) trabajadores (ras) de la salud estuvieron entre los principales grupos de riesgo durante la pandemia de Covid-19, por lo que comprender el perfil de los trabajadores infectados y monitorear la exposición, la enfermedad y la evolución de la enfermedad en el personal permite reconocer los determinantes de las diferentes formas de riesgo y vulnerabilidades relacionadas con la pandemia de Covid-19. El objetivo de este estudio fue describir el perfil epidemiológico de los casos sospechosos de Covid-19 entre los trabajadores de la salud (TS) del estado de Bahía. **Métodos:** Estudio epidemiológico, transversal y descriptivo, con TS, de Bahía, entre mayo de 2020 y diciembre de 2021. Se trata de un censo de trabajadores, con datos según los resultados de las pruebas de Covid-19:positivas, negativas o poco concluyente. **Resultados:** Entre las 45.173 pruebas, el 24,7% tuvieron resultados positivos y el 0,3% no concluyentes, siendo la mayoría mujeres (70,7%), edades entre 33 y 47 años (46,9%), de nivel educativo técnico (45,0%), autodeclaradas. mestizas (61,1%) y trabajo subcontratado (48,2%). No aparecieron diferencias relevantes en el perfil según los resultados de las pruebas. **Conclusión:** Los datos refuerzan la necesidad de monitorear y mejorar las estrategias públicas no solo para la detección, sino también para la protección de los trabajadores de la salud en la lucha contra la pandemia de Covid-19.

Palabras Clave: *Covid-19. Vigilancia de la Salud del Trabajador. Personal de Salud. Salud de los trabajadores. Epidemiología.*

INTRODUCTION

Healthcare workers (HTW) were on the front lines of care for Covid-19 cases and, especially in the first year of the pandemic, until access to vaccination was available, they were among the main risk groups for illness and death from the disease. Healthcare, including medical and hospital services, was considered an essential activity, indispensable to meeting the community's urgent needs, according to Decree 10.2821, from March 20th, 2020, of the Brazilian Federal Government, causing some categories of workers, such as healthcare workers, food production and distribution workers, public safety workers, transportation workers, and urban cleaning workers, among others, to be working in-person under increased risk of exposure to Covid-19 since the most acute phase of the pandemic. Other categories of workers, although not regulated as essential activities, were forced to work in person, as they have historically been part of vulnerable and precarious groups, such as Brazilian domestic workers.[1-4]

Therefore, since the beginning of the Covid-19 pandemic, investments in strategies to protect the health of these workers has become essential to prevent contamination and transmission of Covid-19 in health services and their homes, including the provision of Personal Protective Equipment (PPE), training, testing of suspected cases, use of infection control protocols and early vaccination of workers. Thus, seeking to understand the profile of infected workers and monitoring exposure, illness, and disease progression in the workforce makes it possible to identify the determinants of the different forms of risk and vulnerabilities related to the Covid-19 pandemic and possible cases of Post-Covid Syndrome.[2]

According to the report by the World Health Organization (WHO), by the end of May 2023, 766,895,075 confirmed cases of Covid-19 had been reported in the general population, including 6,935,889 deaths, mainly affecting the regions of Europe and the Western Pacific, followed by the Americas. By September 2020, the year in which the pandemic was declared, Brazil had accumulated a total of 181,886 infected health workers, and among the states, in absolute numbers, Bahia had the highest number of professionals infected by the virus (24,568 cases). The risk of contracting Covid-19 was estimated to be three times higher in SW in the first year of the pandemic, when compared to the general population, although the lethality of the disease in this group was lower, because it depends on other social determinants, such as race/skin color and access to social protection. The estimated prevalence of SARS-CoV-2 infection in health professionals was 11% (95% CI: 7-15) and 7% (95% CI: 4-11), varying by the type of laboratory analysis. Nursing professionals were the most affected (48%, 95% CI: 41-56).[1,5-7]

Despite the current existence of vaccines with more than 13 billion doses administered worldwide, the beginning of the pandemic was marked by the absence of immunizers and effective treatments, with the social distancing strategy being the most effective to prevent the circulation of SARS-CoV-2. However, healthcare workers directly involved in caring for patients infected with Covid-19 were unable to follow these recommendations, constituting a risk group among the general population, being exposed to high viral load and risk of contamination by the disease in their work environment.[8,9]

Among the vulnerabilities that emerged during the pandemic period among workers, there were precarious working and employment conditions, work overload, professional exhaustion and development of mental disorders and other illnesses; the shortage of PPE, the risk of illness and death from the new disease and the possibility of transmission to their family members. In addition to the crisis that demonstrated the precariousness of working conditions and health problems related to work overload, studies have indicated a higher prevalence of long Covid in health workers when compared to other occupations, with prevalence rates reaching 30% of those tested positive for Covid-19.[10-12]

In Brazil, the effects of the pandemic on the health of health workers demanded swift action by municipal and state governments to protect the health and lives of these professionals. However, the lack of guidance from the national health authority, such as a health and safety program for health workers, resulted in specific actions by states and municipalities, especially those with greater management, governance, and budget capacity, which were discontinued with the reduction in the incidence of Covid-19 in the country, especially after the start of vaccination.[4,6]

In Bahia, during the pandemic period, the Directorate of Labor and Education Management and Health (DGTES) of the Bahia State Health Department (Sesab), together with the health surveillance areas, prepared the Sesab Workers' Contingency Plan. It was the country's first plan, which structured a series of actions and strategies for the prevention and protection of health workers working to combat the Covid-19 pandemic. Actions were taken to reorganize services to assist people considered to be suspected and confirmed cases, guidelines were provided for dealing with the disease, and health care flows and actions were implemented for workers in the fight against Covid-19. In addition, testing centers were created to detect Covid-19 and an emergency psychological support service was implemented for workers at the Secretariat and, later, vaccination services.[13]

Therefore, the objective of this study is to describe the epidemiological profile of suspected cases of Covid-19 among health workers in the state of Bahia.

METHODS

This is an epidemiological, cross-sectional and descriptive study, carried out with Sesab workers during the period from May 2020 to December 2021. The time frame was defined considering the availability of data on workers in the state of Bahia. Data collection, carried out by Sesab, was based on the completion of a questionnaire developed by DGETS/Sesab.

Study context

In the state network, DGETS/Sesab is the department responsible for planning and implementing worker health actions, including the Comprehensive Health Care Program for Health Workers (PAIST), acting on the problems of relationships, conditions, links and processes of and at work, contributing to the defense of humanized, dignified and safe working conditions and relationships in the SUS-BA. It is worth noting that during the period of analysis there were 48,894 health workers linked to the state network of Sesab.[14]

Data collection procedures

In order to monitor suspected and confirmed cases of Covid-19, DGETS/Sesab, together with other agencies, implemented the Covid-19 Testing and Reception Center (CTA) and, subsequently, 76 Local Testing Centers (LTC) distributed among the care units, directly and indirectly managed, located in the capital of Bahia, metropolitan region and cities in the interior of the state, seeking to expand the offer of diagnostic tests for the new coronavirus in the population of TS, enabling the monitoring of cases in Bahia.[13]

When tested through the Integrated Workers' Health Care Services (Siast), health workers were submitted to a questionnaire in order to obtain information regarding their health conditions and guide the preparation of the epidemiological bulletins issued by Sesab. In the absence of these, the Health Work Management Centers (Nugtes), the unit's human resources department or even the reference worker were responsible for sending the data to DGETS on a weekly basis.[14]

The study population consisted of health workers from the different Sesab health services, including management workers, such as institutional support workers, those from the Regional Centers and Operational Bases, as well as specialized care services, such as the hospital network and the Emergency network, such as the Mobile Emergency Care Service and Emergency Care Units. This is a case study with workers who were tested for Covid-19. It is worth noting that workers may have been tested on more than one occasion, considering their continuous exposure to the risk of Covid-19 infection during the data collection period. This study considers health workers to be all those who perform their activities or functions in public or private health services, based on the 2005 NOB/RH-SUS reference. The population of SESAB health workers includes 48 occupations, including public health agents, kitchen assistants, engineers, security guards and health professionals, such as nurses and nursing technicians, doctors, and other occupations providing direct health care, which represent the majority of the population. However, it is worth noting that the study did not propose to perform an analysis according to occupations.[15]

The primary data were recorded in a Microsoft Excel spreadsheet, totaling 45,195 records of tests performed on workers. For this research, the criteria for inclusion of the records were: a) data on health workers tested by Siast (including duplicate data due to some workers having more than one employment contract and working in different units, being tested more than once, in different periods). Twenty-one records were excluded if the Covid-19 test result was not provided.

The variables chosen for sociodemographic data were: sex (female and male); age group (17-32 years old, 33-47 years old, 48-62 years old, >63 years old); race/skin color (white, Asian, mixed race, indigenous and black); occupational data, such as: educational background (completed high school, vocational education and higher education), employment relationship (statutory, CLT, outsourced, scholarship holder) and questions related to health conditions and Covid-19 testing. The nine Regional Health Centers of the state were also considered (Central West, Central North, Extreme South, East, Northeast, North, West, Southwest and South). All variables were presented according to the test results (positive, negative and inconclusive).

Data analysis

The data were extracted from the Microsoft Excel platform (version 2017) into the Statistical Package for the Social Sciences (SPSS) program in version 17.0, in which the variables were categorized. A descriptive analysis of the variables was performed, obtaining the simple and relative frequencies for the categorical variables.

Ethical aspects

This study is integrated into the umbrella research entitled “Creation of an Index for Monitoring the Work Environment and Process in Hospitals of the State SUS Network”, and was approved by the Research Ethics Committee of the School of Nursing of the Federal University of Bahia (UFBA) under Certificate of Presentation for Ethical Consideration (CAAE): 38382320.9.0000.5531, and number 4,605,131, with approval date 03/22/2021. The study complied with the

Ethics Criteria for Research with Human Beings, in accordance with Resolution No. 466/2012 of the National Health Council at all stages.

RESULTS

A total of 45,173 Covid-19 tests were recorded among healthcare workers in the state of Bahia, whether symptomatic or not, of which 24.7% had positive results and 0.3% were inconclusive. Of the total number of cases tested, the majority were female (70.7%), aged 33 to 47 years old (47.0%), had a job based on their vocational studies (45.0%) and were outsourced (48.2%). When looking at data on race/skin color, the majority declared themselves to be brown (61.1%), followed by black (21.8%) and white (15.3%). Considering black people as the group of people who declare themselves to be black and brown, the population of black workers represented 82.9% of the total suspected cases tested, as well as 82.3% with a positive test (Table 1).

Table 1. Sociodemographic and occupational characteristics of healthcare workers tested for Covid-19, according to test results, Sesab, Bahia, 2020-2021.

Sociodemographic and occupational characteristics (N)	Positive N (%)	Negative N (%)	Inconclusive N (%)	Total N (%)
Gender				
Female	7.897 (70.7)	23.977 (70.7)	71 (70.0)	31.945 (70.7)
Male	3.278 (29.3)	9.919 (29.3)	31 (30.0)	13.228 (29.3)
Age Group[a]				
17-32 years old	2.673 (26.8)	8.324 (20.5)	30 (0.1)	11.027 (27.2)
33-47 years old	4.704 (47.2)	14.252 (35.2)	49 (0.2)	19.005 (47.0)
48-62 years old	2.375 (23.8)	7.103 (17.5)	17 (0.0)	9.495 (23.4)
>63 years old	219 (2.2)	748 (1.8)	2 (0.0)	969 (2.3)
Functional level[b]				
High School	2.092 (19.5)	6.438 (19.9)	21 (21.4)	8.551 (19.8)
Vocational studies	4.832 (45.1)	14.586 (45.0)	39 (39.8)	19.458 (45.0)
College	3.784 (35.3)	11.372 (35.1)	38 (38.8)	15.194 (35.2)
Race/skin color[c]				
White	1.221 (15.3)	3.788 (15.4)	14 (16.9)	5.023 (15.4)
Asians	186 (2.3)	645 (2.6)	2 (2.4)	833 (2.6)
Browns	4.825 (60.5)	15.082 (61.3)	53 (63.9)	19.960 (61.1)
Indigenous	4 (0.1)	21 (0.1)	0 (0.0)	25 (0.1)
Black	1.742 (21.8)	5.063 (20.6)	14 (16.9)	6.819 (20.8)
Employment bond[d]				
Statutory	2.517 (25.5)	7.699 (25.6)	32 (33.3)	10.249 (25.6)
CLT	2.397 (24.2)	7.186 (23.9)	19 (19.8)	9.602 (24.0)
Outsourced	4.753 (48.1)	14.523 (48.3)	40 (41.7)	19.316 (48.2)
Scholarship holders (student relationship)	221 (2.2)	664 (2.2)	5 (5.2)	890 (2.2)

Abbreviations: [a]Missing data for 4,677 individuals without registration in the age group variable. [b]Missing data for 1,970 individuals without registration in the functional level variable. [c]Missing data for 12,513 individuals without registration in the race/skin color variable. [d]Missing data for 4,677 individuals without registration in the variable.

Among the symptoms presented by suspected cases, headache (14.0%), cough (11.5%) and runny nose (10.3%) were the values that stood out the most, with no difference in expressivity between positive, negative and inconclusive cases (Table 2).

Table 2. Symptoms presented by healthcare workers tested for Covid-19, according to test results, Sesab, Bahia, 2020-2021.

Symptoms	Positive N (%)	Negative N (%)	Inconclusive N (%)	Total N (%)
Headache				
Yes	2.139 (19.1)	4.183 (12.3)	12 (11.8)	6.334 (14.0)
No	9.036 (80.9)	29.713 (87.7)	90 (88.2)	38.839 (86.0)
Cough				
Yes	1.767 (15.8)	3.437 (10.1)	9 (8.8)	5.213 (11.5)
No	9.408 (84.2)	30.459 (89.9)	93 (91.2)	39.960 (88.5)
Runny nose				
Yes	1.535 (13.7)	3.108 (9.2)	12 (11.8)	4.655 (10.3)
No	9.640 (86.3)	30.788 (90.8)	90 (88.2)	40.518 (89.7)
Sore throat				
Yes	1.436 (12.9)	3.097 (9.1)	17 (16.7)	4.550 (10.1)
No	9.739 (87.1)	30.799 (90.9)	85 (83.3)	40.623 (89.9)
Fever				
Yes	1.173 (10.5)	1.948 (5.7)	11 (10.8)	3132 (6.9)
No	10.002 (89.5)	31.948 (94.3)	91 (89.2)	42.041 (93.1)
Sneezing				
Yes	912 (8.2)	1.927 (5.7)	6 (5.9)	2.845 (6.3)
No	10.263 (91.8)	31.969 (94.3)	96 (94.1)	42.328 (93.7)
Fatigue				
Yes	957 (8.6)	1.786 (5.3)	5 (4.9)	2.748 (6.1)
No	10.218 (91.4)	32.110 (94.7)	97 (95.1)	42.425 (93.9)

Symptoms	Positive N (%)	Negative N (%)	Inconclusive N (%)	Total N (%)
Diarrhea				
Yes	708 (6.3)	1.551 (4.6)	6 (5.9)	2.265 (5.0)
No	10.467 (93.7)	32.345 (95.4)	96 (94.1)	42.908 (95.0)
Loss of smell				
Yes	927 (8.3)	1.205 (3.6)	7 (6.9)	2.139 (4.7)
No	10.248 (91.7)	32.691 (96.4)	95 (93.1)	43.034 (95.3)
Loss of taste				
Yes	820 (7.3)	1.043 (3.1)	7 (6.9)	1.870 (4.1)
No	10.355 (92.7)	32.853 (96.9)	95 (93.1)	43.303 (95.9)
Difficulty Breathing				
Yes	429 (3.8)	867 (2.6)	3 (2.9)	1.299 (2.9)
No	10.746 (96.2)	33.029 (97.4)	99 (97.1)	43.874 (97.1)

Considering the clinical profile, it can be observed that 30,541 (67.6%) of the suspected cases had contact with a confirmed case of Covid-19, only 160 (0.4%) were hospitalized and 45,170 (99.9%) out of the suspected cases evolved to cure (Table 3).

Table 3. Clinical characteristics of healthcare workers tested for Covid-19, according to test results, Sesab, Bahia, 2020-2021.

Clinical profile	Positive N (%)	Negative N (%)	Inconclusive N (%)	Total N (%)
Contact with confirmed case				
Yes	7.408 (66.3)	23.071 (68.1)	62 (60.8)	30.541 (67.6)
No	3.767 (33.7)	10.824 (31.9)	41 (39.2)	14.632 (32.4)
Was there hospitalization				
Yes	87 (0.8)	72 (0.2)	1 (1.0)	160 (0.4)
No	11.088 (99.2)	33.823 (99.8)	102 (99.0)	45.013 (99.6)
Outcome (cure/death)				
Cure	11.174 (100.0)	33.894 (100.0)	102 (100.0)	45.170 (100.0)
Death	1 (0.0)	2 (0.0)	0 (0.0)	3 (0.0)

In relation to the records according to Regional Health Centers, the East Center had a higher percentage of testing of suspected cases (64.2%), followed by the Central West Center (11.0%) and the South Center (8.3%) (Table 4).

Table 4. Distribution by Regional Health Centers of health workers tested for Covid-19, according to test results, Sesab, Bahia, 2020-2021.

Regional Health Center	Positive N (%)	Negative N (%)	Inconclusive N (%)	Total N (%)
Midwest	1.181 (10.9)	3.594 (11.0)	10 (10.2)	4.785 (11.0)
Midwest North	199 (1.8)	786 (2.4)	3 (3.1)	988 (2.3)
Far South	198 (1.8)	585 (1.8)	0 (0.0)	783 (1.8)
East	6.968 (64.2)	20.898 (63.9)	64 (65.3)	27.930 (64.0)
Northeast	122 (1.1)	439 (1.3)	2 (2.0)	563 (1.3)
North	202 (1.9)	613 (1.9)	1 (1.0)	816 (1.9)
West	240 (2.2)	869 (2.7)	1 (1.0)	1.110 (2.5)
Southwest	790 (7.3)	2.254 (6.9)	6 (6.1)	3.050 (7.0)

Abbreviations: [a]Missing data for 1,525 individuals without registration in the Regional Health Center variable.

DISCUSSION

The epidemiological profile of health workers tested for Covid-19 at Sesab was characterized by a higher incidence of females, young adults, black people, vocational workers, outsourced workers and those working in services at the Eastern Regional Center, where the state capital is located. Most cases had contact with a suspected case and were cured without the need for hospitalization, regardless of the test result.

The female profile is the most representative in health occupations, which is equivalent to approximately 70% of health and social service work teams. Considering the feminization of the health workforce, the conditions of greater exposure to the risk of contamination by Covid-19 and the accumulation of working hours, it is assumed that female workers presented a greater risk and vulnerability to illness from Covid-19.[4,16]

Regarding age group, the young adult population, economically active, with less social protection and possibility of social distancing, was the most affected group. In addition, there is a low representation of SW in the age group over 63 years old, due to the mandatory removal of SW over 60 years old from their work activities, according to Ordinance No. 52 of 03/12/2020, who are considered part of the high-risk group for developing severe forms of the disease and deaths.[17]

Regarding self-declared race/skin color among SW, the contingent of black people (83%), when black and brown people are added, is consistent with the population characteristics of the state of Bahia. According to the Continuous National Household Sample Survey (PNADC), carried out in June 2022, among the 15 million Bahians, 80.8% were black people, 23.9% were black people, and 56.9% were brown people. This study highlights a higher frequency of suspected and tested cases of Covid-19 among the black population, including black women, compared to

other nationwide studies with healthcare workers and the general population or conducted in other states, which present a total number of suspected cases more representative in the self-declared white population, which may also reflect the invisibility of black healthcare workers. The association between black race/skin color and increased risk for Covid-19 was the strongest evidence found in a literature review on the social determinants related to the incidence of the disease, based on findings from three large observational studies conducted with the general population, without a specific focus on occupation.[18-20]

Regarding the functional level, the largest sample was observed among vocational workers. This result may be related to the nature of the activities performed by these professionals, which may involve direct and prolonged contact with patients. The literature points to disparities between the different categories of healthcare professionals, showing that vocational workers, for example, may face specific risk conditions, even when their functions are not directly related to healthcare.[21]

The prevalence of Covid-19 found in the population of the present study, of 24.7%, was higher than that found in other studies with healthcare workers, as well as the prevalence of asymptomatic individuals (who did not present any of the symptoms investigated), of approximately 80%, was also higher than that of previous studies. As in the population of healthcare workers at Sesab, fever and cough were the most frequent symptoms in the findings of previous studies with healthcare professionals. In a systematic review with meta-analysis, it was observed that among health professionals who tested positive for Covid-19, 40% (95% CI: 17-65) were asymptomatic at the time of diagnosis, and, among those who were symptomatic, the most frequent symptoms were fever (56%, 95% CI: 50-64), dry cough (57%, 95% CI: 50-65), malaise (43%, 95% CI: 26-61) and myalgia (48%, 95% CI: 35-62). Serious clinical complications developed in 5% (95% CI: 3-8) of health professionals who tested positive for Covid-19 and 0.5% (95% CI: 0.02-1.3) died.[1,22]

Considering the distribution of Covid-19 cases by location, the Eastern Regional Health Center had a higher percentage of suspected and tested cases. The Eastern region includes the city of Salvador, the state capital, with a significant population density, representing 19.1% of the population of the state of Bahia. Thus, the volume of cases of community transmission in this territory stands out, as well as a greater concentration of health services and hospitals, with a significant number of health workers in relation to other cities in the state.[13]

The State Government adopted measures to deal with the emergency in Bahia in March 2020, where employees were 60 years old or over, with a history of respiratory and chronic diseases, pregnant women and those using immunosuppressive medications, due to greater risk, began to work remotely. In this study, it can be observed that only 3 of the suspected cases of Covid-19 evolved to death, and this number can be justified by the removal of more vulnerable health workers, and, based on Technical Note No. 53 of the Bahia Health Emergency Operations Center, by better access to health services and the protection provided, such as the distribution of PPE and testing, by the services.[23,24]

Among the suspected cases, the outsourced relationship was noticeable as being more expressive among workers, which may be related both to the outsourcing process in Public Health and to the precariousness and vulnerability of these workers, when compared to statutory workers. In Bahia, temporary hiring has increased, surpassing the percentage of public career workers in 2022. Workers with temporary employment bond represented 37.0% of jobs in establishments linked to the SUS, compared to 34.0% of public career workers. Although the population of this study is diverse, including all workers involved in all activities of health services, such as security guards, receptionists and direct health care professionals, it is recognized that the majority of the population are vocational workers or health assistants, followed by those with higher education.[25]

Among the limitations of the study, a significant frequency of under-reporting of information and missing data was observed, due to the lack of a pilot experience, in addition to the lack of training of professionals to fill out the spreadsheet due to the state of emergency in obtaining this data, which may interfere with the quality of the results. However, the results presented allow for the understanding of information that characterizes the occurrence of the disease among health workers and its relationship with working conditions and may serve as a subsidy for assistance policies for the protection and prevention of worker health.

Therefore, it is essential to strengthen the continuous monitoring of influenza-like syndromes in health services, as well as to improve and ensure adherence to individual and collective protective measures, aiming at the prevention of new cases and the mitigation of severe forms of Covid-19 among health workers. The implementation of strategies aimed at reducing the exposure of the most vulnerable professionals, such as older professionals, should be considered a priority in the formulation of health policies, especially given the possibility of new epidemics.

In addition, promoting health equity requires the adoption of measures that ensure effective protection for black workers, outsourced workers and vocational workers, groups that face additional challenges due to structural inequalities. Addressing these vulnerabilities

requires the formulation of specific policies, the strengthening of supervision in health institutions and the development of continuous actions to ensure safer and fairer work environments. Thus, by expanding the perspective on these inequalities, and on occupation in health, the study contributes to the improvement of institutional strategies for prevention and protection of health workers, reinforcing the commitment to the safety, equity and appreciation of these essential workers.

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AUTHORS' CONTRIBUTIONS

Sara de Santana Vieira contributed to the writing of the abstract, introduction, methodology, construction of results and discussion, and final review. **Rafaella Santiago Coutinho Santos** contributed to the analysis and interpretation of results,

writing and critical review of content. **Milena Maria Cordeiro de Almeida** contributed to data analysis, construction of results and discussion, completion of the text, and final review. **Samilly Silva Miranda** contributed to planning, organization of the database, analysis, and review of the text. **Handerson Silva Santos** contributed to data analysis, completion of the text, and final review. **Luciano de Paula Moura** contributed to completion of the text and final review. **Bruno Guimarães de Almeida** contributed to the conception and design of the study. **Tatiane Araújo dos Santos** contributed to the final review.

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

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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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Original Article

Spatial distribution and temporal behavior of the Zika virus in the municipality of Araguaína/Tocantins, 2016 to 2023

Distribuição espacial e comportamento temporal do vírus Zika no município de Araguaína/Tocantins, 2016 a 2023
Distribución espacial y comportamiento temporal del virus Zika en el municipio de Araguaína/Tocantins, 2016 a 2023

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Corresponding author:
E-mail: nicolaskevyn77@gmail.com
Address: Fourteenth of January Street, No. 982 – São João, Araguaína, Tocantins, Brazil.

Nicolas Kevyn Cavalcante Fernandes[1]
Helierson Gomes[2]

[1]Medicine Program, Federal University of Northern Tocantins (UFNT), Araguaína, Tocantins, Brazil.
[2]Epidemiology Laboratory, Federal University of Northern Tocantins (UFNT), Araguaína, Tocantins, Brazil.

ABSTRACT

Background and Objectives: To analyze the spatial epidemiological distribution of Zika virus infections and its temporal behavior in the municipality of Araguaína, state of Tocantins, Brazil, emphasizing the relevance of continuous surveillance and control and prevention methods. **Methods:** Ecological study of time series and trends of confirmed Zika virus cases in the municipality of Araguaína-TO. The seasonal pattern of the disease was assessed using a control chart containing indices per year and levels by epidemiological week. Spatial analysis data were distributed with the help of QGIS software by neighborhoods, delineating high and low-risk clusters. **Results:** The municipality reported 2,031 cases during the assessed period with 519 confirmed, showing a stationary trend with low indices and a seasonal pattern. The most affected individuals were female, of mixed ethnic background, aged between 20 and 39 years, with less than 12 years of schooling. The disease exhibited heterogeneous characteristics within the municipality, affecting both large demographic centers and peripheral neighborhoods. **Conclusion:** Understanding the epidemiological characteristics is important for promoting public policies and health education aimed at developing mechanisms for predicting outbreaks, as well as strategies for controlling infections to reduce and/or prevent new epidemics of this arbovirus through interdisciplinary action.

Keywords: *Zika Virus. Epidemiology. Spatial Analysis. Ecological Studies.*

RESUMO

Justificativa e Objetivos: Analisar a distribuição epidemiológica espacial das infecções pelo vírus Zika e seu comportamento temporal no município de Araguaína, estado do Tocantins, Brasil, enfatizando a relevância da vigilância contínua e métodos de controle e prevenção. **Métodos:** Este foi um estudo ecológico de séries temporais e tendência dos casos confirmados de vírus Zika no município de Araguaína-TO. O padrão sazonal da doença foi avaliado pelo diagrama de controle, contendo índices por ano e níveis por semana epidemiológica. Os dados de análise espacial foram distribuídos com o auxílio do software QGIS por bairros, delimitando clusters de alto e baixo risco. **Resultados:** O município relatou 2.031 casos no período avaliado, sendo 519 confirmados, com uma tendência estacionária de baixos índices e padrão sazonal. Os indivíduos mais afetados foram do sexo feminino, pardos, idade entre 20 e 39 anos, e nível de escolaridade inferior a 12 anos de estudo. A doença apresentou características heterogêneas dentro do município, afetando tanto grandes centros demográficos, quanto bairros periféricos. **Conclusão:** O discernimento acerca das características epidemiológicas é importante para promover políticas públicas e educação em saúde destinadas ao desenvolvimento de mecanismos de previsão de surtos, além de estratégias para o controle das infecções, visando reduzir e/ou sanar novas epidemias dessa arbovirose através da interdisciplinaridade de atuação.

Descritores: *Zika Vírus. Epidemiologia. Análise Espacial. Estudos Ecológicos.*

RESUMEN

Justificativa y Objetivos: Analizar la distribución epidemiológica espacial de las infecciones por el virus del Zika y su comportamiento temporal en el municipio de Araguaína, estado de Tocantins, Brasil, enfatizando la importancia de la vigilancia continua y los métodos de control y prevención. **Métodos:** Estudio ecológico de series temporales y tendencias de los casos confirmados de virus del Zika en el municipio de Araguaína-TO. El patrón estacional de la enfermedad fue evaluado mediante un gráfico de control que contenía índices por año y niveles por semana epidemiológica. Los datos de análisis espacial fueron distribuidos con la ayuda del software QGIS por barrios, delimitando clústeres de alto y bajo riesgo. **Resultados:** El municipio reportó 2.031 casos durante el período evaluado, de los cuales 519 fueron confirmados, mostrando una tendencia estacionaria con índices bajos y un patrón estacional. Los individuos más afectados fueron mujeres, de origen étnico mixto, con edades entre 20 y 39 años y un nivel educativo inferior a 12 años de estudio. La enfermedad presentó características heterogéneas dentro del municipio, afectando tanto a grandes centros demográficos como a barrios periféricos. **Conclusión:** El conocimiento sobre las características epidemiológicas es importante para promover políticas públicas y educación en salud dirigidas al desarrollo de mecanismos para la predicción de brotes, así como estrategias para el control de las infecciones, con el objetivo de reducir y/o prevenir nuevas epidemias de esta arbovirosis mediante la acción interdisciplinaria.

Palabras Clave: *Virus Zika. Epidemiología. Análisis Espacial. Estudios Ecológicos.*

INTRODUCTION

Arboviruses are considered pathologies of viral etiology transmitted by arthropods, mainly by hematophagous mosquitoes of the genera *Aedes*, *Culex* and *Lutzomyia*, and are an eminent global public health problem. To date, only a few arboviruses cause clinically significant human diseases and are transmitted by mosquitoes, including *Alphaviruses* such as Chikungunya, and *Flaviviruses* such as Zika, Dengue and West Nile.[1,2]

The ability to adapt to new environments, vectors and hosts through viral mutation and genetic plasticity imposed by environmental changes caused by anthropogenic action, increased international exchange and climate change, gives these microorganisms the potential to cause widespread outbreaks and epidemics. These changes have a direct impact on the transmissibility of these zoonotic infections, allowing the mosquito vector to live closer to humans and spread to new areas.[1,2]

Zika is an important arbovirus disease caused by the Zika virus (ZIKV), which is responsible for clinical manifestations such as arthralgia, myalgia, fever, maculopapular rash, conjunctivitis, and others. It was initially isolated in West Africa in the late 1940s and remained restricted to the African continent until 2007, when it attracted global attention due to an outbreak in Micronesia. From there, the virus spread to other Pacific islands, emerging as a generalized epidemic in Latin America. In 2015, it arrived in Brazil through infected travelers serving as reservoirs for transmission by the *Aedes aegypti* mosquito and sexual or transplacental activity, and then, reports of a mild disease began to increase in the Brazilian northeast.[3,4]

It is estimated that from 2015 to the end of 2016, more than 1.6 million cases of this arbovirus occurred in the country. The Northeast region concentrated the largest number of cases, followed by the Central-West and North regions. In 2016 alone, 10,867 cases were reported, of which 2,366 were confirmed, and of these, 200 deaths were recorded, determining a fatality rate of 8.5% for the disease. Regarding the notification of this arbovirus disease in the state of Tocantins, the capital Palmas had the highest proportion of cases with values above 200/100,000 inhabitants.[5–7]

In addition, the SARS-CoV-2 pandemic, the novel coronavirus 2019 (Covid-19), directly impacted the epidemiological patterns of ZIKV, mainly by diverting resources and attention from epidemiological surveillance to combating the coronavirus. With the overload of health systems, there was a reduction in the notification of cases and monitoring of arbovirus diseases, making it difficult to accurately assess the incidence of ZIKV during this period. In addition, measures such as social isolation and reduced population mobility may have indirectly influenced the transmission of ZIKV by altering contact between humans and vectors. This repercussion highlights the need to maintain continuous and integrated surveillance, even in health emergency scenarios.[8]

In this context of dissemination, a dramatic increase in cases of microcephaly, Guillain-Barré syndrome, meningoencephalitis and myelitis was detected among newborns, in addition to other congenital manifestations (congenital Zika syndrome), such as musculoskeletal and ocular malformations. A causal relationship was established between ZIKV infection and its teratogenic effect with tropism for developing nerve cells, leading the Brazilian Ministry of Health and the World Health Organization to declare a Public Health Emergency of National and International Concern.[7,9,11]

Even though knowledge about this disease has advanced and now there is possibility of serological diagnoses and prophylaxis against the vector, it still represents a potential challenge for public health due to the unavailability of vaccines as a prophylactic method or effective antivirals for the treatment of a disease that can be fatal or incapacitating. Additionally, the economic impact can be presumed, since repercussions after the acute phase, such as neurological disorders with generalized muscle weakness and paralysis, interfere with occupational activities.[2,12]

It is also important to highlight that the possibility of other manifestations arising from the coinfection of ZIKV with other diseases cannot be ruled out. Although the lethality of ZIKV infection is low, the fact that most infected people are asymptomatic contributes to its spread and may be associated with the emergence of new cases and outbreaks. Therefore, it is not possible to exclude the need for new investigations, nor the continuous work of entomological and epidemiological surveillance of healthcare in detecting and monitoring cases in order to establish methods for controlling and preventing this disease.[2,5,11]

Given this situation, this study proposes to carry out a spatial epidemiological analysis of reported cases of ZIKV infection in the municipality of Araguaína, state of Tocantins, from 2016 to 2023.

METHODS

This is an ecological time series analytical study of confirmed cases of ZIKV infection in the period from 2016 to 2023 in the municipality of Araguaína, northern region of the state of Tocantins.

Considered the second most populous city in the state according to the last Census, the municipality has an estimated population of 171,301 inhabitants in a total area of 4,004.646 km², subdivided into 124 neighborhoods.[13]

The region is currently a major economic center with privileged logistics and federal highways that contribute to the city's intense interpersonal traffic. The city is also considered a reference and health center for neighboring municipalities, which may impact the spread of vectors and/or diseases imported into the municipality.

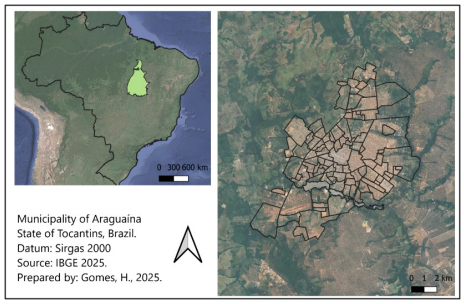

Figure 1. Municipality of Araguaína, State of Tocantins, Brazil. Source: Gomes et al, 2025.

In the development of the study, all confirmed cases of Zika in the municipality were analyzed, excluding inconclusive or probable cases without confirmation. Epidemiological data on confirmed cases of Zika, as well as sociodemographic and clinical characteristics were collected through the Health Information System provided by DATASUS through Tabnet. Information regarding the Building Infestation Index (BII) was provided by the health department of the municipality of Araguaína through the arbovirus department. Data were organized, processed and statistically analyzed using Excel and the Statistical software for data science (Stata MP-64).

The BII is a metric widely used in public health surveillance to assess the degree of infestation by vectors, such as *Aedes aegypti*. This index is calculated based on the proportion of properties in which the breeders of these vectors are identified in relation to the total number of properties inspected in a specific area. Infestation rates were categorized as follows: 0 to 1% (low risk), 1 to 3.99% (alert), and greater than 3.99% (high risk). The variations observed were organized according to the average infestation rates during the study period, providing a comprehensive and detailed view of the dynamics of the infestation in the municipality.[14]

First, the analyzes were performed by converting the absolute case values into incidence using the following formula: confirmed cases of the disease divided by the population at risk, multiplied by one hundred thousand.[15]

The control chart was designed to analyze the risk levels of disease progression with analysis of the rates per year (2016 to 2023) and later of the levels per epidemiological week (52) of the post-pandemic biennium to determine the seasonal pattern of the disease in the municipality.[14]

To analyze the concentration of cases, a cartographic map with the division of the neighborhoods of the municipality of Araguaína was generated, in which information on the incidence of the disease was inserted. The incidence was represented using the proportional symbols technique, which adjusts the size of circles according to the density of the occurrence of the phenomenon of interest. The values of the BII by neighborhood were represented choroplethically using a color scale according to the different risk levels. Data organization, spatial analyzes and generation of the final map layout were performed using the Quantum GIS (QGIS) software, allowing a clear and precise visualization of the variables analyzed.

As this is open-access public domain information and investigators have no access to sensitive data, the study was not submitted to the Human Research Ethics Committee (CEP) for evaluation, in accordance with CNS Resolution No. 510 of 2016, article 2, VI.

RESULTS

During the years of the study, the city of Araguaína reported 2,031 cases of ZIKV in SINAN. Of these, only 519 cases were confirmed, with emphasis on the years 2016 and 2017, which together represented more than 90% of notifications.

Regarding the epidemiological profile, women had a higher incidence (67.43%), a higher percentage of cases occurred in individuals of mixed ethnic background (81.69%), young adults in the age group 20-39 years (46.24%), with a maximum education of nine to 12 years (38.92%). Of the total confirmed cases, 99.03% evolved to cure (Table 1).

Table 1. Sociodemographic and clinical characteristics and evolution of confirmed cases of Zika virus in the municipality of Araguaína-TO from 2016 to 2023.

Characteristic	N (%)	P
Female	350 (67.44)	
Male	169 (32.56)	0.002
Total	519 (100)	
Age range (in years)		
0-4	27 (5.2)	
5-9	24 (4.62)	
10-19	94 (18.11)	
20-39	240 (46.24)	0.0001
40-59	120 (23.12)	
≥ 60	12 (2.31)	
Unknown	2 (0.38)	
Race/skin color		
White	72 (13.87)	
Black	8 (1.54)	
Yellow	3 (0.57)	
Mixed ethnic background	424 (81.69)	<0.0001
Indigenous	4 (0.77)	
Unknown	8 (1.54)	
Education in years		
0	2 (0.38)	
< 9	172 (33.14)	
9-12	202 (38.92)	0.003
> 12	83 (15.99)	
Unknown	23 (4.43)	
Not applicable	37 (7.13)	
Evolution		
Cure	518 (99.04)	
Death	1 (0.19)	< 0.0001
Unknown/blank	4 (0.77)	

According to the control chart for Zika incidence in the period evaluated (Figure 2), there was a stationary trend dynamic with low rates. Most cases described for the years 2022 and 2023 were concentrated between epidemiological weeks 9 and 25, reflecting the seasonality of this arbovirus.

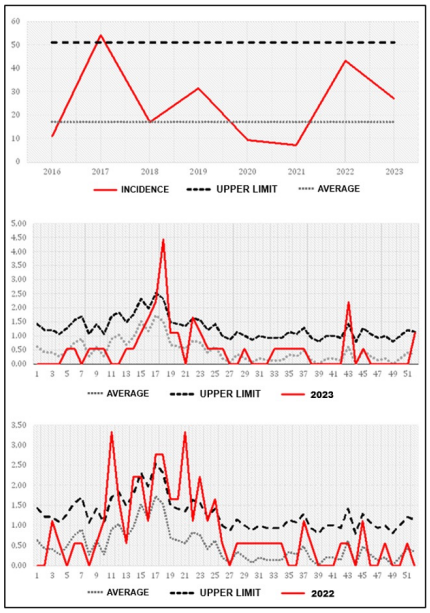

Figure 2. Control chart for Zika incidence for the period 2016 to 2023 and according to epidemiological week for the years 2022 and 2023 (incidence per 100,000 inhabitants).

Regarding the spatial distribution pattern, the manifestation of this arbovirus disease presented heterogeneous characteristics within the municipality. The centers with the highest population densities were some of the areas at high risk for transmission, according to the BII, with emphasis on the neighborhoods of Araguaína Sul, São João and the central sector.

Despite the varied presentation in the territory, much of the incidence was also focused on some peripheral regions with socio-environmental characteristics favorable to the spread of *A. aegypti*, mainly Lago Azul 1 and 2, Jardim Filadélfia and Bairro Senador (Figure 3).

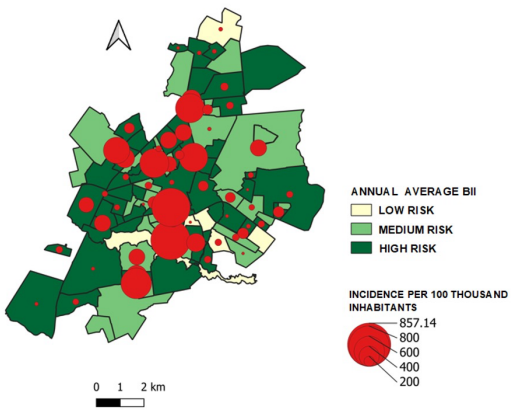

Figure 3. Zika incidence levels and annual average building infestation rate by neighborhood in the municipality of Araguaína, state of Tocantins.

DISCUSSION

The city of Araguaína has historically been known for fluctuations in rainfall and air temperature, presenting favorable conditions for the spread of arboviruses transmitted by the *A. aegypti* mosquito. In addition, its strategic spatial position between the states of Pará and Maranhão together with economic centers such as the cities of Marabá-PA, Imperatriz-MA and the capital Palmas-TO, and intercity land transport may favor an epidemiological corridor between different ecosystems, contributing to the migratory dynamics of infections.[16,17]

In this study, the epidemiological pattern of ZIKV infection in the city was concentrated in females and the age group of 20-39 years, although it can affect the entire population at different ages.[18] The phenomenon described as “feminization of poverty” may reflect a household profile of women, mainly in the most peripheral areas of the city, favoring greater contact with the vector. Furthermore, some studies suggest that women, because they take greater care of their health, generally seek more medical care than men, and may not be the most affected by the disease but contribute more to notifications.[19,20]

Therefore, underreporting is still a common phenomenon in Brazil, which may occur due to diagnostic errors, asymptomatic infections and problems in accessing health services. In fact, the similarity of symptoms between arboviruses (Dengue, Zika and Chikungunya) and the benign and self-limiting nature of most ZIKV infections may interfere with the diagnosis. Thus, the lower incidence in men may also be justified by their low demand for healthcare in the face of an oligosymptomatic disease. This fact can be mitigated with strategies aimed at this public, such as the National Men’s Health Program created by the Ministry of Health, educational campaigns aimed at primary care, such as the Blue November, and encouragement of routine care and preventive health in the workplace as well.[21]

The noticeable discrepancy between the most affected age groups, more common in the economically active population aged between 20 and 39 years old, followed by the range between 40 and 59 years can be explained by the greater movement of these people in their work activities and contact with different risk environments. Furthermore, the prevalence in lower levels of education can be justified by difficulties in understanding and managing preventive measures, contributing to the increase in suspected cases.

Similar to previous ecological studies, in the present study, a positive association between ZIKV infection and residents who self-identify as mixed ethnic background was observed.[22] Currently, some evidence suggests that both social origin and race interfere in income inequality in our country, with repercussions on

access to essential services, such as health, education and employment. In the scenario of infectious diseases, this reality may reflect greater vulnerability of a certain portion of the population, such as people of mixed ethnic background, as they often live in more exposed areas to vectors and face barriers in accessing preventive and care measures. However, public policies such as *Bolsa Família* and other income transfer programs have played an important role in mitigating this disparity, improving living conditions and consequently reducing the incidence of diseases.[23,24]

It is also noteworthy that according to the 2022 IBGE Census, the majority of the Brazilian population (45.3%) declared themselves as being of mixed ethnic background, providing a large contingent of susceptible individuals.[25]

Regarding the temporal distribution of cases, a greater number of notifications was observed in the first epidemiological weeks, reflecting the seasonal nature of the rain in the region, providing hot and humid climates with suitable environments that accelerate the vector's reproductive cycle, in line with research in other cities such as Teresina-PI and Goiânia-GO.[22] It is well known that inadequate water treatment, precarious sewage systems and accumulation of stagnant water increase soon after the start of the rainy season. These data reinforce the need to intensify vector control campaigns and personal protective care at this time of year.

Most notifications occurred in the early years of the epidemic in Brazil, between 2016 and 2017, with sporadic cases remaining at a steady level in the following years, which suggests a certain effectiveness in the implementation of public policies to control the disease. Among these measures, the importance of the joint participation of Community Health Agents (CHA), Endemic Disease Control Agents (ACE), zoonosis agents and the population itself stands out. Identifying and controlling potential mosquito breeding sites, personal protection with repellents, and continuing health education have a positive impact on reducing transmission.[26]

The spatial distribution analysis showed a diverse characteristic of affected areas, spreading throughout the region and maintaining a higher incidence in some neighborhoods in the city center and the outskirts.[27] There was a tendency for notification in areas of greater population density with vegetation and a nearby lake, such as in the Lago Azul 1 and 2 sectors, Jardim Filadélfia and Bairro Senador, where there is peridomicile habitat for vectors, facilitating mosquito-human contact and making the population more susceptible. Some studies have also identified that neighborhoods close to water reservoirs, such as lakes and streams, were more affected by arboviruses.[28,29]

It is a fact that the process of urbanization and verticalization of the city associated with inadequate infrastructure increased residual waste, and a dynamic population migration favors closer coexistence between humans and mosquitoes. It is suggested that cities with better economic indicators and higher population density have a high prevalence of arboviruses (Dengue, Zika and Chikungunya), a phenomenon observed in the two largest cities in Tocantins (Araguaína and Palmas).[19]

Although health and selective collection coverage are good, this is justified in central and more agglomerated areas, since the high population density associated with the production of non-organic waste, irregular disposal of litter on the streets and around homes, construction waste and a large flow of people, facilitate the spread of the disease by acting as possible temporary breeding grounds for the mosquito.[26,30,31]

The heterogeneity of affected locations observed in this study may suggest that the daily movement of individuals to central neighborhoods, whether for work or leisure activities, has a positive impact on the infection that affects the most remote areas of the city, since when individuals return to their homes, they can contribute to the spread. Although the behavioral profile of some arboviruses has been reported in previous studies, a flow analysis, evaluating the likely infection environment and the place of residence could provide more information about the role of local population mobility in the spread of infections by vector mosquitoes.[20]

This study presents relevant results, but some limitations arising from the use of secondary data must be considered. It was not possible to include variables related to income, social vulnerability index and selective waste collection, restricting the analysis of the interaction between socio-environmental and economic factors, which may have compromised the identification of more comprehensive patterns. Added to this is the potential for underreporting, since asymptomatic or oligosymptomatic patients may not seek health services or live in areas of poor offer of these services, which may underestimate the real magnitude of the phenomenon investigated.

It is essential to consider these limitations during the interpretation of results, recognizing the need for future studies using primary data in order to minimize these biases.

However, this study advances knowledge and its contributions will certainly support the establishment of new public policies and health education aimed at preventive measures, prioritizing public resources for regions of the city with higher risks and incidence of cases. Therefore, interdisciplinarity in the fight against this arbovirus, addressing issues of health, environment and other fields of knowledge, becomes of utmost importance for the control of ZIKV infections by offering a more comprehensive view of the problem.

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AUTHORS' CONTRIBUTIONS

Nicolas Kevyn Cavalcante Fernandes contributed to bibliographic research, data collection, processing and analysis, writing, content development and critical review of the manuscript. **Helierson Gomes** contributed to the conception and design of the study, methodology, interpretation and description of results, statistics, image processing, relevant critical review of the manuscript and approval of the final version to be published.

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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

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Original Article

Epidemiological profile of people with type 2 diabetes and characterization of the foot: a cross-sectional study

Perfil epidemiológico de pessoas com diabetes tipo 2 e caracterização do pé: um estudo transversal
Perfil epidemiológico de las personas con diabetes de tipo 2 y caracterizacióndel pie: unestudio transversal

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Corresponding author:
E-mail: luisianeas@gmail.com
Address: Pau Brasil Avenue, Lot 05, Águas Claras, Brasília, Federal District, Brazil.

Mayanne Soares Camilo[1]
Maria da Graça Moreira Lorena[1]
Carol Lima Barros[1]
Felipe Macedo Soares[2]
Juliana Alburquerque Baltar[1]
Luísiane de Ávila Santana[1]

[1]University of Brasilia, Brasilia, Federal District, Brazil.
[2]Federal University of Jataí, Jataí, Goiás, Brazil.

ABSTRACT

Background and Objectives: To identify more vulnerable population groups and guides preventive actions, the study aimed to understand the epidemiological profile, characterize the foot and identify the presence of neuropathy in individuals with type 2 diabetes at an outpatient clinic in the Federal District. **Methods:** This was a cross-sectional, quantitative and descriptive study. Data were collected through therapeutic evaluation and analysis of medical records of people with type 2 diabetes at the Specialized Outpatient Clinic of the Health Department of the Federal District, in the period between 2022 and 2023, using convenience sampling. **Results:** 67 people were included, of whom were female 35 (52,2%), elderly 41 (61,1%) and on a low income 47 (64,1%). The following characteristics were observed: glycated hemoglobin ≥7% (87,5%) and the presence of integumentary and circulatory alterations. In addition, 31 (46,2%) of the individuals showed signs of diabetic peripheral neuropathy. **Conclusion:** It was observed that women, the elderly and people on low incomes had diabetes in a state of decompensation, and almost half of the sample had peripheral neuropathy.

Keywords: *Diabetes Mellitus, Type 2. Epidemiology. Secondary Care. Diabetic Neuropathies. Diabetic Foot.*

RESUMO

Justificativa e Objetivos: Para identificar grupos populacionais mais vulneráveis e direcionar ações preventivas, o estudo teve como objetivo conhecer o perfil epidemiológico, caracterizar o pé e identificar a presença de neuropatia em indivíduos com diabetes tipo 2 em um ambulatório no Distrito Federal. **Métodos:** Estudo transversal, quantitativo e descritivo. Os dados foram coletados através de avaliação terapêutica e análise de prontuários de pessoas com diabetes tipo 2 do Ambulatório Especializado da Secretaria de Saúde do Distrito Federal, no período entre 2022 e 2023, a partir de amostragem por conveniência. **Resultados:** Foram incluídos 67 pessoas, sendo a maioria do sexo feminino 35 (52,2%), idosos 41 (61,1%) e baixa renda 47 (64,1%). Observou-se as seguintes características: hemoglobina glicada ≥7% (87,5%) e destacou-se a presença de alterações tegumentares e circulatórias relacionadas ao exame do pé. Além disso, 31 (46,2%) dos indivíduos apresentaram sinais de neuropatia periférica diabética. **Conclusão:** Observou-se que mulheres, idosos e pessoas de baixa renda apresentaram diabetes em estado de descompensação, quase metade da amostra apresentou neuropatia periférica.

Descritores: *Diabetes Mellitus Tipo 2. Epidemiologia. Atenção Secundária à Saúde. Neuropatias Diabéticas. Pé Diabético.*

RESUMEN

Justificación y Objetivos: Para identificar grupos de población más vulnerables y dirigir acciones preventivas, el estudio tuvo como objetivo comprender el perfil epidemiológico, caracterizar el pie e identificar la presencia de neuropatia em indivíduos con diabetes tipo 2 em um ambulatório del Distrito Federal. **Método:** Se trata de un estudio transversal, cuantitativo y descriptivo. Los datos se recolectaron a través de la evaluación terapéutica y el análisis de las historias clínicas de las personas con diabetes tipo 2 en la Consulta Externa Especializada de la Secretaría de Salud del Distrito Federal, en el período comprendido entre 2022 y 2023, utilizando un muestreo de conveniencia. **Resultados:** Fueron incluidas 67 personas, siendodel sexo femenino 35 (52,2%), ancianos 41 (61,1%) y de baja renta 47 (64,1%). Se observaronlassiguientes características: destacaba una hemoglobina glucosilada ≥7% (87,5%) y la presencia de alteraciones tegumentarias y circulatorias. Además, 31 (46,2%) de los individuos presentaban signos de neuropatía periférica diabética. **Conclusión:** Se observó que las mujeres, los ancianos y las personas con bajo singresostenían diabetes en estado de descompensación, y casi la mitad de la muestra presentaba neuropatía periférica.

Palabras Clave: *Diabetes Mellitus Tipo 2. Epidemiología. Atención Secundaria de Salud. Neuropatías Diabéticas. Pie Diabético.*

INTRODUCTION

Diabetes Mellitus is a metabolic condition characterized by the loss of glycemic homeostasis that culminates in chronic hyperglycemia, due to insufficient production and/or action of the hormone insulin.[1,2] In 2021, in the 10th edition of the International Diabetes Federation – Diabetes Atlas, it was estimated that 537 million adults aged between 20 and 79 years lived with diabetes in the world, and this number is expected to increase to 783 million by 2045. In the same period, in Brazil, there were approximately 15.7 million people living with diabetes, a prevalence of 10.5% in the adult population, therefore, it is a health problem of great epidemiological relevance.[1]

Currently, there are several types of diabetes, however, type 2 Diabetes Mellitus stands out, which accounts for approximately 90 to 95% of all cases of diabetes, characterized by the progressive loss of insulin secretion combined with insulin resistance, which leads to a state of chronic hyperglycemia.[3] The World Health Organization defines that chronic hyperglycemia is associated with significant micro and macrovascular complications, increased morbidity, reduced quality of life and increased mortality rates among people with diabetes.[4] It is also known that the development of complications related to diabetes is associated with both cultural, economic and social changes and the aging of the population.[5] In addition, the costs of diabetes and its complications have been increasing exponentially every year, directly impacting the Unified Health System and Brazilian society.[6]

Among the complications caused by diabetes, diabetic foot stands out, which manifests itself through infections, ulcerations and/or destruction of soft tissues and is considered the main cause of non-traumatic amputation of the lower limbs.[2] This occurs due to diabetic peripheral neuropathy that affects the peripheral nervous system and presents as a diffuse, symmetrical, distal and progressive lesion of the sensory-motor and autonomic fibers.[7] It is believed that diabetic peripheral neuropathy occurs due to chronic hyperglycemia which, in short, in the long term, causes changes in insulin balance that lead to a partial reduction in the activity of neuronal growth factors, which impacts the formation of neurofilaments and maintenance of axonal transport, leading to axonal degeneration and apoptosis of the neuronal body, causing neuropathy to gradually set in. In addition, diabetic foot can occur due to cardiovascular factors related to hyperglycemia, such as reduced blood flow, increased vascular resistance and decreased oxygen tension.[8]

Diabetic peripheral neuropathy is diagnosed clinically and is based on altered neurological tests or signs, based on the evaluation of fine nerve fibers (thermal and pain sensitivity and sudomotor function) and coarse nerve fibers (tendon reflexes, vibration and tactile sensitivity). The tests for checking for alterations in coarse fibers include: Diabetic Peripheral Neuropathy-Check, Bioesthesiometer, 10g Semmes-Weinstein Monofilament and 128 Hz Tuning Fork. And, for coarse and fine fibers: Modified Toronto Score, Neuropathic Impairment Score, Michigan Score and for fine fibers the NeuroPad test.[7]

Based on this, knowing the epidemiological profile of people with Type 2 Diabetes Mellitus is important to understand the distribution of risk factors related to the disease, as well as the tracking and monitoring of diabetic peripheral neuropathy through specific tests useful in the prevention and progression of the disease and, based on a clinical and functional diagnosis, it is possible to consider the best approach for individuals. Therefore, this study aims to characterize the epidemiological profile and identify the presence of neuropathy in individuals with type 2 diabetes, in an outpatient clinic in the Federal District.

METHODS

This is a cross-sectional, quantitative and descriptive study. Data collection was carried out at a Specialized Outpatient Clinic of the Health Department of the Federal District. The study obtained its data through convenience sampling from the outpatient clinic's own appointments for foot assessments of individuals with diabetes, during the years 2022 and 2023. People with diabetes, already scheduled for the outpatient clinic, were invited to participate in the project. After acceptance, they were informed about the ethical issues and, after signing the term, the pre-established assessments and analysis of medical records began.

Regarding the eligibility of the study population, the inclusion criteria were: people with type 2 diabetes, of both genders, who were over 18 years old with at least 5 years since the diagnosis. Besides this, the exclusion criteria were: active ulcers on the feet at the time of the assessment, amputation of the lower limb and/or incomplete medical records. Two forms were used during data collection. The first was the "*Functional Assessment of the Diabetic Foot*", which is an adapted form that contains variables related to sociodemographic characteristics: gender, age, self-reported skin color, education, occupation, family income, and marital status. The following are also related to clinical characteristics: time since diagnosis, weight, height, body mass index, glycated hemoglobin, blood glucose monitoring, associated diseases, and medications.[3,4,7]

The second is the "*Form for Assessment of Neuropathy and Peripheral Arterial Disease*", which is a form used by the outpatient clinic itself to diagnose diabetic peripheral neuropathy and peripheral arterial

disease. This study used the following variables: Skin aspects (Dry skin, cracks, fissures; Altered skin color; Mycoses (interdigital and nail); Absence of hair; Calluses). Structural aspects (High-arched foot; Collapsed arch; Valgus; Claw toes; Reduced joint mobility; Previous ulcer). Neurological aspects (Absent 10g monofilament in any area of the test; Absent Achilles reflex (reflex hammer); Diminished or absent sensitivity (vibration, pain and heat). Circulatory aspects (Edema; Dilated dorsal vessels; Diminished or absent bilateral pulses (posterior tibial and pedal).[3,4,7]

With this form it was also possible to establish the Neuropathic Symptom Score and the Neuropathic Impairment Score, the latter being recommended by the Brazilian Diabetes Society for the definitive diagnosis of diabetic peripheral neuropathy. The first score is scored through questions related to the most frequent symptoms and the second is scored based on neurological tests, which were tested on both feet, with the subject's eyes closed, so that there would be no interference in the result.[7] All procedures were performed after invitation, consent and signing of the Free and Informed Consent Form.

The collected data were typed and organized in spreadsheets using a double-entry validation technique. For analysis, the information was distributed in tables containing the quantitative variables with calculation of absolute and relative frequency, mean and standard deviation. For the qualitative variables, the absolute and relative frequency values were calculated. Microsoft Office Excel 10® software and the EPI INFO program version 7.2.5.0 were used.

This study was approved on January 31st, 2022 by the Institutional Ethics Committee of the University of Brasília and the Foundation for Teaching and Research in Health Sciences through opinion number 5,217,470.

RESULTS

Although there were 80 recruited individuals, and due to the eligibility criteria, 13 individuals were excluded for the following reasons: active foot ulcer (4), lower limb amputation (4), and failure to complete the assessment (5). Finally, 67 individuals with Type 2 Diabetes Mellitus were included.

The sociodemographic variables that presented the highest percentages were: female gender (52.2%), age ≥60 years (61.1%), self-declared white skin color (38.8%), complete or incomplete primary education (50.7%), retired (59.7%), family income between one and two minimum wages (64.1%), and married marital status (61.1%) (Table 1).

Table 1. Descriptive analysis of sociodemographic variables of the Outpatient Clinic of the Health Department of the Federal District, 2022-2023.

Variables	N (%)	Mean (standard deviation)
Gender (n=67)		
Female	35 (52.2)	
Male	32 (47.7)	
Age (n=67)		62.6 (±8.24)
< 60 years old	26 (38.8)	
≥ 60	41 (61.1)	
Self-declared skin color (n=67)		
Yellow	3 (4.4)	
White	26 (38.8)	
Brown	16 (23.8)	
Other	2 (2.9)	
Black	20 (29.8)	
Education (n=67)		
Illiterate	7 (10.4)	
Complete or incomplete primary education	34 (50.7)	
Complete or incomplete secondary education	16 (23.8)	
Complete or incomplete higher education	10 (14.9)	
Occupation (n=67)		
Retired	40 (59.7)	
Unemployed	10 (14.9)	
Employed	17 (25.3)	
Family income (n=67)		
1 to 2 minimum wages	47 (64.1)	
3 to 4 minimum wages	9 (13.4)	
More than 4 minimum wages	15 (22.3)	
Marital Status (n=67)		
Married	41 (61.1)	
Divorced	6 (8.9)	
Single	12 (17.9)	
Widow	8 (11.9)	

The clinical variables that stand out are: time since diagnosis ≥10 years (82.0%), mean body mass index of 29.1 kg/m² (standard deviation ±5.7) with most people being overweight (43.2%), mean glycated hemoglobin of 8.8% (standard deviation ±1.7) with a predominance of glycated hemoglobin ≥7% (87.5%), capillary blood glucose monitoring <3 times a day (77.6%) and use of insulin (94.0%). Among the comorbidities associated with diabetes, hypertension stands out (71.6%) (Table 2).

Table 2. Descriptive analysis of clinical variables at the Outpatient Clinic of the Health Department of the Federal District, 2022-2023.

Variables (n=67)	N (%)	Mean (standard deviation)
Time since diagnosis (n=67)		16% (±7.62)
< 10 years	12 (17.9)	
≥ 10 years	55 (82.0)	
Weight (n=67)		77.7 (±16.4)
High (n=67)		1.63 (±0.1)
Body Mass Index (n=67)		29.15 (±5.7)
Normal	14 (20.9)	
Overweight	29 (43.2)	
Grade I Obesity	15 (22.3)	
Grade II Obesity	6 (8.9)	
Grade III Obesity	3 (4.4)	
Glycated hemoglobin (n=67)		8.8 (±1.7)
< 7%	8 (12.5)	
≥ 7%	56 (87.5)	
Glycemic monitoring (n=67)		
< 3x per day	52 (77.6)	
≥ 3x per day	10 (14.9)	
does not monitor	5 (7.4)	

Variables (n=67)	N (%)	Mean (standard deviation)
Associated comorbidities (n=67)		
Hypertension	48 (71.6)	
Dyslipidemia	26 (38.8)	
Former smoker	12 (17.9)	
Medications (n=67)		
Diabetes	57 (86.3)	
Cholesterol	36 (54.5)	
Hypertension	34 (50.7)	
Insulin	63 (94.0)	

Regarding the results related to the examination of the diabetic foot, among integumentary and structural characteristics, the following stand out: dry, cracked or fissured skin (95.5%), calluses (89.5%), nail mycosis (65.6%), in addition to limited joint mobility (47.7%). Regarding neurological characteristics, most of the volunteers (55.2%) had reduced or absent vibratory sensitivity, and 19 (28.3%) were classified as neuropathic through the 10g Semmes-Weinstein Monofilament test. Regarding the circulatory characteristics with the highest percentage were: dilated dorsal vessels (65.6%), decreased or absent right posterior tibial pulse (50.7%), decreased or absent left posterior tibial pulse (49.2%), decreased or absent pedal pulses in both feet (22.3%). Among the subjects who presented changes in their pulses, only six underwent the Ankle-Brachial Index test. Furthermore, only 1 (1.4%) person presented changes suggestive of cardiovascular disease risk due to the Ankle-Brachial Index result being >1.30º, which suggests the presence of calcification. The others were within the normal range without the presence of peripheral arterial disease (Table 3).

From this, through the score obtained with the evaluation of the Achilles reflex, vibration, pain and temperature, a total of 31 (46.2%) people with signs of diabetic peripheral neuropathy (>2) were observed, of which 23 (34.3%) presented mild signs, 8 (11.9%) presented moderate signs and no subject presented severe neuropathic signs, according to the Neuropathic Impairment Score.

Table 3. Descriptive analysis of foot characterization and identification of neuropathic signs at the Outpatient Clinic of the Health Department of the Federal District, 2022-2023.

Variables	N (%)
Skin aspects	
Dry skin, cracks, fissures (n=67)	64 (95.5)
Changes in skin color (n=67)	12 (17.9)
Interdigital mycosis (n=67)	15 (22.3)
Ungual mycosis (n=67)	44 (65.6)
Absent hair (n=67)	24 (35.8)
Calluses (n=67)	60 (89.5)
Structural aspects	
High-arched foot (n=67)	5 (7.4)
Collapsed arch (n=67)	1 (1.4)
Valgus (n=67)	23 (34.3)
Claw toes (n=67)	20 (29.8)
Limited joint mobility (n=67)	32 (47.7)
Previous ulcer (n=67)	11 (16.4)
Neurological aspects	
Monofilament 10g absent in any test area (n=67)	19 (28.3)
Absent Achilles reflex (n=67)	19 (28.3)
Decreased or absent vibratory sensitivity (n=67)	37 (55.2)
Decreased or absent pain sensitivity (n=67)	15 (22.3)
Decreased or absent thermal sensitivity (n=67)	15 (22.3)
Circulatory aspects	
Edema (n=67)	16 (23.8)
Dorsal dilated vessels (n=67)	44 (65.6)
Decreased or absent right posterior tibial arterial pulse (n=67)	34 (50.7)
Decreased or absent left posterior tibial arterial pulse (n=67)	33 (49.2)
Decreased or absent right dorsalis pedis pulse (n=67)	15 (22.3)
Decreased or absent left dorsalis pedis pulse (n=67)	15 (22.3)
Change in ankle-brachial index (n=67)	1 (1.4)
Neuropathic Sign Score	
Normal (0-2)	36 (53.7)
Mild (3-5)	23 (34.3)
Moderate (6-9)	8 (11.9)
Severe (9-10)	0 (0.0)

Regarding the occurrence of neuropathic symptoms, there was a predominance of burning, numbness or tingling (61.1%), in the feet (61.1%), at night (49.2%) and, to alleviate the symptoms, the volunteers walked (61.1%). At the time of collection, more than half of the people were using inadequate footwear (53.7%). Based on the score obtained through the Neuropathic Symptom Score, the majority had severe symptoms (37.3%) (Table 4).

Table 4. Descriptive analysis of the identification of neuropathic symptoms at the Outpatient Clinic of the Health Department of the Federal District, 2022-2023.

Variables	N (%)
Neuropathic symptoms	
Burning, numbness, or tingling (n=67)	41 (61.1)
Fatigue, cramping, or pain (n=67)	17 (25.3)
Asymptomatic (n=67)	9 (13.4)
Most common location of symptoms	
Feet (n=67)	41 (61.1)
Legs (n=67)	17 (25.3)
Other (n=67)	9 (13.4)
Time of day when symptom occurs	
Night (n=67)	33 (49.2)
Day and night (n=67)	18 (26.8)
Day (n=67)	16 (23.8)
Have you ever woken up at night because of the symptom (n=67)	27 (40.3)
What relieves the symptom?	
Walking (n=67)	41 (61.1)
Standing up (n=67)	11 (16.4)
Sitting or lying down (n=67)	15 (22.3)
Inappropriate footwear (n=67)	36 (53.7)
Neuropathic Symptom Score	
Normal (0-2)	10 (14.9)
Mild (3-4)	10 (14.9)
Moderate (5-6)	22 (32.8)
Severe (7-9)	25 (37.3)

DISCUSSION

In the present study, it was observed that the majority of the sample was composed of women, which is similar to other findings in the literature, in studies that also characterize the epidemiological profile of people with Type 2 Diabetes Mellitus, treated in outpatient services, in which the percentage of more than 70% is composed of women. One of these findings was carried out in a

reference center in Aracaju - Sergipe and the other in an Endocrinology Outpatient Clinic of the Lauro Wanderley University Hospital, located in João Pessoa – Paraíba.[9,10] This can be attributed to the fact that women diagnosed with diabetes are the main users of health services, due to a greater concern regarding their own health when they present physical signs and symptoms of diseases.[10,11] In addition, elderly individuals aged ≥60 years are predominant in seeking medical services, considering that this is the period of life most affected by complications caused by type 2 diabetes.[10]

It is believed that the low level of education seen among diabetics may be associated with modifiable risk factors, such as sedentary behavior, physical activity, BMI, smoking, and excessive television watching. A study conducted with the population of the United Kingdom demonstrated that directly intervening in the educational level contributes to the efficiency in improving health and reducing mortality.[12] A study conducted in João Pessoa - Paraíba is similar in that most of the individuals studied were elderly, retired, and with an income between 1 and 2 minimum wages, which corresponded to approximately more than 50% of the sample.[10] This fact may compromise the ability of elderly people to maintain care for a good diet, use of medications, undergo periodic examinations, issues that imply in the preservation of health and, directly, in the control of the disease.[10] It was identified in the sample that the majority were married, suggesting that marital cohabitation may be beneficial and perhaps contribute to health care, enabling chances of success in treatment and self-care.[10]

The predominance of time since diagnosis ≥10 years was quite pronounced, and the literature states that this may influence the treatment of these subjects, since, due to the longer time since diagnosis, it is assumed that experience with the disease provides more information about the pathology. On the other hand, the longer time may lead to a lack of motivation to follow diabetes care, as a consequence of the lack of effective results, given the chronic condition.[13] According to the World Health Organization classification, overweight individuals have a body mass index greater than 25 kg/m².[14] In this study, a considerable percentage was classified as overweight, which corroborates the literature, which indicates that obesity has a high prevalence in all age groups of both sexes and on a global scale, being a consequence of unhealthy diets, lack of physical activity and environmental factors.[15] In other words, obesity is one of the main risk factors, especially visceral obesity, thus aggravating cardiovascular risk and disturbances in glucose-insulin homeostasis.

It is considered that the diabetic individual with the greatest need for glycemic control is the one with glycated hemoglobin values ≥7%, this being an indirect measurement of glycemia used as a predictor parameter to avoid complications.[2] In this study, the average glycated hemoglobin values were higher, and it is described in the literature that the association between long-term glucose variability can induce cardiovascular complications. Oxidative stress, low-grade inflammation and endothelial dysfunction can be the main drivers.[16] Therefore, it is recommended that these people undergo laboratory tests at least every quarter to better control the disease.[2] For adults with Type 2 Diabetes Mellitus using basal insulin or oral hypoglycemic agents, there is little evidence on the number of capillary blood glucose tests required daily. However, it is suggested that capillary blood glucose monitoring in people undergoing insulin treatment be performed at least four times a day, demonstrating that the greater frequency of capillary blood glucose monitoring is associated with improved glycated hemoglobin.[2] Systemic Arterial Hypertension was observed in most individuals with type 2 diabetes.

In these cases, intensive blood pressure control is suggested, since the treatment of hypertension in diabetic individuals is a protective factor for micro and macrovascular outcomes.[2] Therefore, the coexistence of chronic diseases such as hypertension and diabetes is indicated as an important risk factor for systemic complications, increasing the percentage of mortality and generating higher costs for the health system.[17] A Korean study points to a high rate of patients with diabetes mellitus and hypertension, since hypertension is associated with a higher risk of heart failure, atrial fibrillation, chronic kidney disease, valvular and coronary heart disease, dementia and stroke, and adequate control of hypertension is necessary.[18]

Based on the descriptive analysis of the foot examination, dry skin, with cracks or fissures, as well as calluses and nail fungus stand out. The literature describes that dry skin and calluses can occur from ineffective care, such as not using oils or moisturizing creams and wearing inappropriate footwear. Thus, it is known that some daily care for the feet of individuals with diabetes is necessary to prevent such aspects. However, in the sample, risk factors for the development of diabetic foot were observed, thus corroborating a study that presents data similar to this one, with the main comorbidities found being dry feet, calluses and cracks.[19]

Mycoses were one of the most common findings, with nail mycosis being the most frequent, followed by interdigital mycosis. These results are similar to the findings of other authors who demonstrated similar data and that, despite the diagnosis of Type 2 Diabetes Mellitus, some foot care is not performed effectively, emphasizing the need for better training and approach of health professionals regarding foot care, as well as

encouraging the practice of self-care in individuals with Diabetes Mellitus.[20]

Valgus and limited joint mobility may contribute to the increased risk of plantar ulceration, since they are associated with higher plantar pressure. A study shows that limited joint mobility is what promotes the highest rate of high plantar pressure, thus increasing the risk of ulceration when related to the existence of diabetic peripheral neuropathy.[21] Regarding loss of sensitivity, the present study shows that among the individuals evaluated, more than half have reduced or absent vibratory sensitivity, which demonstrates the importance of assessing this to identify risk factors and reduce the chances of amputation.[20]

In this study, the percentage of dilated dorsal vessels and reduced or absent right/left posterior tibial arterial pulse stand out. In other words, they are directly related to the high risk of foot ulceration and lower limb amputation.[22] The most frequent neuropathic symptoms in the sample were burning, numbness or tingling in the lower limbs, especially the feet, during the night. This confirms data from the literature that show the same neuropathic symptoms, and these can negatively influence the individual's quality of life or even nighttime disorders.[23]

Regarding the relief of symptoms of diabetic peripheral neuropathy, the most frequently reported variable was walking, followed by sitting or lying down. This supports the hypothesis of another study that presented physical activity as one of the viable non-pharmacological interventions, where a combination of resistance and sensorimotor training presents greater benefits for symptoms.[24] Thus, demonstrating that non-pharmacological strategies should not be underestimated.

None of the subjects were classified as having peripheral arterial disease, which may be related to the fact that it was not possible to perform the Ankle-Brachial Index test on all of them, due to problems with the unit's Doppler ultrasound. This is different from the findings of another study that indicates individuals with type 2 diabetes mellitus and peripheral arterial disease in a more severe manifestation, where patients have a higher prevalence of coronary artery disease, including risks to the lower limbs.[25] However, the vast majority of the sample presented changes in the pulses, which should be frequently monitored.

In the present study, a greater number of individuals diagnosed with diabetic peripheral neuropathy were also observed using the Neuropathic Impairment Score, in relation to the 10g Semmes-Weinstein Monofilament test. In the literature, a similar result was identified in an elderly population, using the same assessment instruments, in which it was seen that the 10g monofilament alone is capable of indicating the decrease or absence of protective sensitivity, which can generate plantar ulceration; however, it is not recommended that it be used alone for the diagnosis of diabetic peripheral neuropathy.[26]

Therefore, it is concluded that this study made it possible to understand the profile of people with type 2 diabetes, which is described as being composed, in its majority, of elderly women with low income, low level of education and with clinical characteristics of decompensated diabetes, which highlights the presence of glycated hemoglobin ≥7% and hypertension, conditions that are risk factors for the development and progression of diabetic peripheral neuropathy. In addition, important changes related to the feet were found, such as: dry skin, cracks and fissures, calluses, reduced joint mobility, reduced or absent vibratory sensitivity, dilated dorsal vessels and reduced posterior tibial pulses, aspects seen in the literature as a risk for ulceration and amputation. And, finally, through the use of the Neuropathic Impairment Score and Neuropathic Symptom Score for the diagnosis of diabetic peripheral neuropathy, it was possible to observe the presence of neuropathy with moderate and severe symptoms.

This study does not allow establishing cause and effect relationships due to its observational nature. The findings of this study can be used to develop preventive and management strategies for diabetes and diabetic foot; it is recommended that subsequent studies be carried out.

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AUTHORS' CONTRIBUTIONS

Mayanne Soares Camilo has substantially contributed to the design and planning of the project, data collection, analysis and interpretation of data; contributed significantly to the preparation of the draft and critical review of the content. **Maria da Graça Moreira Lorena** has substantially contributed to the design and planning of the project, data collection, analysis and interpretation of data; has also significantly contributed to the preparation of the draft and

critical review of the content. **Carol Lima Barros** has contributed to data collection, analysis and interpretation of data. **Felipe Macedo Soares** has contributed with the summary writing and the content critically reviewing. **Juliana Alburquerque Baltar** has contributed to the writing of the text and the preparation of tables. **Luísiane de Ávila Santana** has substantially contributed to the design and planning of the project, data collection, analysis and interpretation of data; contributed significantly to the preparation of the draft and critical review of the content.

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

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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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Original Article

Antimicrobial switch therapy: barriers and facilitators from the perspective of nurses, pharmacists and physicians

Transição de via de antimicrobianos: barreiras e facilitadores na perspectiva de enfermeiros, farmacêuticos e médicos
Conversión de la vía antimicrobiana: barreras y facilitadores desde la perspectiva de enfermeras, farmacéuticos y médicos

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Corresponding author:
E-mail: tativaleriano@yahoo.com.br
Address: Franscislo Lopes Street, 200, Santa Felicia Park, Sao Carlos, Sao Paulo, Brazil.

Tatiane Garcia do Carmo Flausino[1,2]
Darlyani Mariano da Silva[1]
Lívia Cristina Scalon da Costa Perinoti[1,3]
Rosely Moralez de Figueiredo[1]

[1]Federal University of São Carlos, Postgraduate Program in Nursing. São Carlos, São Paulo, Brazil.
[2]University Hospital of the Federal University of São Carlos (HU-UFSCar). São Carlos, São Paulo, Brazil.
[3]University Center of Associated Teaching Colleges, São João da Boa Vista, São Paulo, Brazil.

ABSTRACT

Background and Objectives: The antimicrobial switch therapy is an easy-to-implement intervention that can generate savings in resources and nursing service time and contribute to the impact of antimicrobial resistance. However, it does not occur at the right time for hospitalized patients. Thus, the objective of this study is to identify the barriers and facilitators of the antimicrobial switch therapy from the perspective of these nurses, pharmacists, and physicians. **Methods:** This is an online survey study, descriptive and quantitative, conducted in the city of São Carlos, São Paulo, Brazil, with nurses, pharmacists, and physicians working in a hospital environment. Data collection was done through an online questionnaire. A descriptive analysis of the data was performed using absolute and relative frequency tables. **Results:** A total of 167 participants answered the questionnaire, of which 79 were pharmacists, 71 were nurses, and 17 were physicians. The main barriers identified by the participants were the lack of medication with adequate oral bioavailability, lack of engagement of prescribers, and oral medication not available at the institution. The facilitators were the possibility of hospital discharge, hospital infection control service operating at the institution, and cost. **Conclusion:** The present study identified the barriers and facilitators that contribute to the development of institutional strategies within the antimicrobial stewardship programs, enabling the switch therapy to occur at an opportune time and safely.

Keywords: *Antimicrobial Stewardship. Drug Administration Routes. Drug Resistance. Microbial. Surveys and Questionnaires.*

RESUMO

Justificativa e Objetivos: A transição de via de antimicrobianos da endovenosa para oral é uma intervenção de fácil implementação, capaz de gerar economia de recursos, de tempo de serviço da enfermagem e contribuir para o impacto da resistência antimicrobiana, entretanto, ela não acontece no momento oportuno para os pacientes hospitalizados. Face ao exposto, o objetivo deste estudo é identificar as barreiras e facilitadores da transição de via de antimicrobianos sob a perspectiva de enfermeiros, farmacêuticos e médicos. **Métodos:** Estudo do tipo *survey online*, descritivo e de abordagem quantitativa, realizado no município de São Carlos, São Paulo, Brasil, com enfermeiros, farmacêuticos e médicos assistenciais que atuam em ambiente hospitalar. A coleta de dados foi feita a partir da disponibilização de questionário *online*. Foi realizada análise descritiva dos dados, a partir de tabelas de frequência absoluta e relativa. **Resultados:** Responderam o questionário 167 participantes, sendo 79 farmacêuticos, 71 enfermeiros e 17 médicos. As principais barreiras apontadas pelos participantes foram ausência de medicamento com biodisponibilidade oral adequada, falta de engajamento dos prescritores e medicamento via oral não disponível na instituição. Já os facilitadores foram a possibilidade de alta hospitalar, serviço de controle de infecção hospitalar atuante na instituição e custo. **Conclusão:** O presente estudo identificou as barreiras e facilitadores que contribuem para a elaboração de estratégias institucionais dentro dos Programas de Gerenciamento de Antimicrobianos, possibilitando que a transição de via aconteça em momento oportuno e com segurança. As principais barreiras encontradas incluem a ausência de opção oral com biodisponibilidade adequada e falta de engajamento dos prescritores. A redução de custos, possibilidade de alta precoce e presença de comissão de controle de infecção hospitalar atuante foram os principais facilitadores encontrados.

Descritores: *Gestão de antimicrobianos. Vias de administração de medicamentos. Resistência microbiana a medicamentos. Inquéritos e questionários.*

RESUMEN

Justificación y Objetivos: La transición de la vía antimicrobiana intravenosa a la oral es una intervención de fácil implementación, capaz de ahorrar recursos, tiempo del servicio de enfermería y contribuir al impacto de la resistencia a los antimicrobianos, sin embargo, no ocurre en el momento adecuado para los pacientes hospitalizados. Por tanto, el objetivo de este estudio es identificar las barreras y facilitadores de la transición de la ruta antimicrobiana desde la perspectiva de estos enfermeros, farmacéuticos y médicos. **Métodos:** Estudio de encuesta online, descriptivo y con abordaje cuantitativo, realizado en la ciudad de São Carlos, São Paulo, Brasil, con enfermeros, farmacéuticos y médicos clínicos que actúan en el ambiente hospitalario. La recopilación de datos se realizó mediante la puesta a disposición de un cuestionario en línea. El análisis descriptivo de los datos se realizó mediante tablas de frecuencia absoluta y relativa. **Resultados:** Respondieron al cuestionario 167 participantes, 79 farmacéuticos, 71 enfermeros y 17 médicos. Las principales barreras destacadas por los participantes fueron la falta de medicamentos con biodisponibilidad oral adecuada, la falta de compromiso de los prescriptores y los medicamentos orales no disponibles en la institución. Los facilitadores fueron la posibilidad de alta hospitalaria, el servicio de control de infecciones hospitalarias que opera en la institución y el costo. **Conclusión:** El presente estudio identificó las barreras y facilitadores que contribuyen al desarrollo de estrategias institucionales, dentro de los Programas de Optimización del Uso de los Antimicrobianos, permitiendo que la transición se lleve a cabo de manera oportuna y segura.

Palabras Clave: *Programas de Optimización del Uso de los Antimicrobianos. Vías de Administración de Medicamentos. Farmacorresistencia Microbiana. Encuestas y Cuestionarios.*

INTRODUCTION

Antimicrobial resistance (AMR) is a major cause of mortality, contributing to approximately 9% of all global deaths. In middle- and low-income countries, the effects of AMR-related morbidity and mortality are more severe, which could impact the loss of about 5% of the gross domestic product of these locations by 2050, exacerbating the situation of extreme poverty.[1]

Antimicrobials have been considered an indispensable resource in the treatment of previously fatal infections for decades. However, their excessive, improper, and inappropriate use has contributed to AMR and jeopardized the effectiveness of this class of drugs.[2]

In this context, Antimicrobial Stewardship Programs (ASP) have emerged as a strategy to combat and mitigate AMR.[1] Among the strategies for optimizing the use of antimicrobials in ASPs is the early transition from intravenous (IV) to oral administration(OA).[3] The transition of antimicrobial route (TAR) in patients who meet eligibility criteria enables the reduction of costs, hospitalization time, nursing work hours, the use of invasive devices, and Adverse Events (AE) associated with infusion therapy, in addition to greater patient mobility and autonomy.[4]

However, despite the benefits of early TAR, it is common for patients who meet the eligibility criteria for TAR to receive the entire course of therapy parenterally, remaining hospitalized for treatment. In fact, among hospitalized patients who meet the criteria for TAR, in 45-75% of cases, the transition is not performed.[5]

It should be noted that nurses, pharmacists, and infectious disease physicians are key professionals, along with clinical microbiologists, in the composition of the ASP management team.[6] They are directly related to antimicrobial therapy.

In this sense, the following research question was structured: "What are the barriers and facilitators of TAR from the perspective of nurses, pharmacists, and physicians?" Identifying barriers and facilitators could contribute to safe and timely TAR, enabling the transposition of identified barriers and the enhancement of facilitators. Thus, the objective of this study is to identify the barriers and facilitators of antimicrobial route transition from the perspective of these professionals.

METHODS

An online survey was conducted, which was descriptive and quantitative in nature, based on the recommendations set out in the Enhancing the Quality and Transparency of Health Research Network (Equator Network) platform, using the Checklist for Reporting Results of Internet E-Surveys (CHERRIES) tool, which is specifically designed for observational survey studies conducted via the internet.[7]

To identify the barriers and facilitators of TAR from the perspective of nurses, pharmacists, and physicians, a questionnaire-type data collection instrument was developed, whose content was defined based on the results of the previous stage of this study, which included interviews with key professionals (nurses, pharmacists, and infectious disease physicians), as well as data from a literature review.[8-9]

The questionnaire was reviewed at a research group meeting and pre-tested with one representative from each professional category. There were no changes to the instrument after the pre-test stage, only spelling adjustments.

The final version of the instrument consisted of 20 multiple-choice questions organized into the following domains: participant characteristics (five questions covering professional category, area of practice, length of experience, region of practice, and prior knowledge of ASP); knowledge about ASP and TAR (seven questions); barriers to route transition (one question); facilitators of route transition (one question); contribution of professionals to TAR (four questions); and criteria for TAR (two questions).

The eligibility criteria included nurses, pharmacists, and physicians working in hospitals, with no limitation on the length of service or training of these professionals. Professionals working exclusively in management were excluded.

The questionnaire was available for completion from April 1, 2022, to August 6, 2022. Strategies for dissemination, invitation, and recruitment of potential research participants were carried out in social media groups (Instagram®, Facebook®, and LinkedIn®). All professionals who met the eligibility criteria at the national level were considered potential participants, and the study sample was non-probabilistic. This study identified the barriers and facilitators that contribute to the development of institutional strategies within Antimicrobial Stewardship Programs, enabling the transition to occur in a timely and safe manner.

This research was conducted in accordance with the ethical standards required by Resolutions 466/2012, 510/2016, and 580/2018 of the Ministry of Health and was approved by the Research Ethics Committee (REC) under opinion number 5.142.045 and registration CAAE 51677721.0. 000.5504 on December 2, 2021. All those who agreed to participate in the research signed the Free and Informed Consent Form (FICF).

RESULTS

A total of 167 participants responded to the questionnaire, of whom 79 (47.3%) were pharmacists, 71 (42.5%) were nurses, and 17 (10.2%) were

physicians. In terms of the geographical origin of the respondents, there was a predominance of participants from the southeast region with 124 participants (74.3%), followed by the midwest region with 14 participants (8.4%), the south region with 13 participants (7.8%), the northeast region with 11 participants (6.6%), and the north region with five participants (3.0%).

Regarding the length of experience in the hospital context, 24 participants (14.4%) had up to two years of experience, followed by 44 participants (26.3%) with between two and five years of experience, 40 participants (24%) with between six and 10 years of experience, and 24 (35.3%) with more than 10 years of experience. The participants' areas of practice are listed below (Table 1).

Table 1. Participants' area of activity. São Carlos, SP, Brazil, 2022 (n=167).

Area of expertise	N (%)
Clinical Pharmacy	53 (31.7)
Hospital Pharmacy	43 (25.7)
Intensive Care Unit	37 (22.2)
Other	36 (21.6)
HICS*	33 (19.8)
Emergency Room/Urgent Care Unit	23 (13.8)
Medical Clinic Unit	21 (12.6)
Oncology Unit	7 (4.2)
Surgical Clinic Unit	6 (3.6)

Abbreviations: * HICS: Hospital Infection Control Service.

Regarding respondents' familiarity with the topic of ASP, it is noteworthy that 14% of respondents were unfamiliar with the term. The results are shown below (Figure 1).

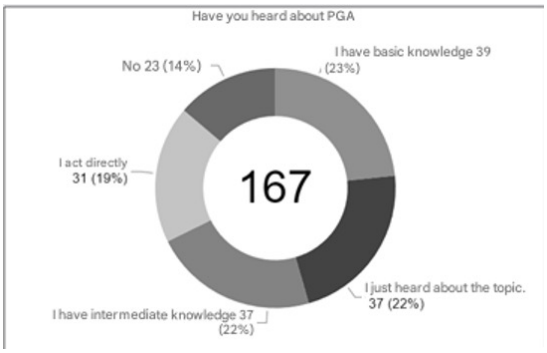

Figure 1. Knowledge about the topic Antimicrobial Stewardship Programs. São Carlos. SP. Brazil, 2022.
Abbreviations: ASP: Antimicrobial Stewardship Programs

With regard to knowledge about ASP and TAR, it is noteworthy that 143 (86%) participants agree that the discussion with the prescriber for TAR can be initiated by either a nurse or a pharmacist. On the other hand, 46 participants (28%) pointed out that TAR, although economical, can contribute to the worsening of the patient's condition, since they consider that oral medications do not have the same potency or efficacy (Table 2).

Table 2. Knowledge about antimicrobial stewardship programs and antimicrobial transition pathways. São Carlos, São Paulo, Brazil, 2022. (n=167).

Domain 1: questions 1 to 6					
Question	Completely agree N (%)	Agree N (%)	Disagree N (%)	Completely disagree N (%)	I don't want to answer N (%)
1) To work in ASP*, nurses, pharmacists, and doctors need basic knowledge about microbial resistance and the smart use of antimicrobials	129 (77.2)	32 (19.2)	4 (2.4)	1 (0.6)	1 (0.6)
2) Although other professionals can contribute to ASP*, nurses, pharmacists, and physicians can directly contribute to the transition of antimicrobial routes	124 (74.3)	40 (24.0)	2 (1.2)	0 (0.0)	1 (0.6)
3) The IV†/OA‡ transition generates savings, but does not impact the reduction or control of resistance	26 (15.6)	62 (37.1)	59 (35.3)	18 (10.8)	2 (1.2)
4) The IV†/OA‡ transition is an intervention that can be discussed with the prescriber by both nurses and pharmacists	69 (41.3)	74 (44.3)	19 (11.4)	5 (3.0)	0 (0.0)
5) The IV†/OA‡ transition is economical, but has the disadvantage of contributing to the patient's worsening condition, as medications administered orally do not have the same potency/efficacy as intravenous medications	15 (9.0)	31 (18.6)	72 (43.1)	48 (28.7)	1 (0.6)
6) To be eligible for route transition, the patient must meet specific conditions, such as hemodynamic stability, absence of fever spikes, and preserved swallowing ability	87 (52.1)	66 (39.5)	12 (7.2)	1 (0.6)	1 (0.6)

Abbreviations: *ASP: antimicrobial stewardship program. †IV: intravenous. ‡OA: oral.

As for barriers to TAR (Figure 2), the absence of oral medication with adequate bioavailability was highlighted by 127 (76%) participants, the lack of engagement by prescribers was pointed out by 124 (74%) participants, and the unavailability of oral medication equivalent to parenteral medication was pointed out by 123 (74%) participants.

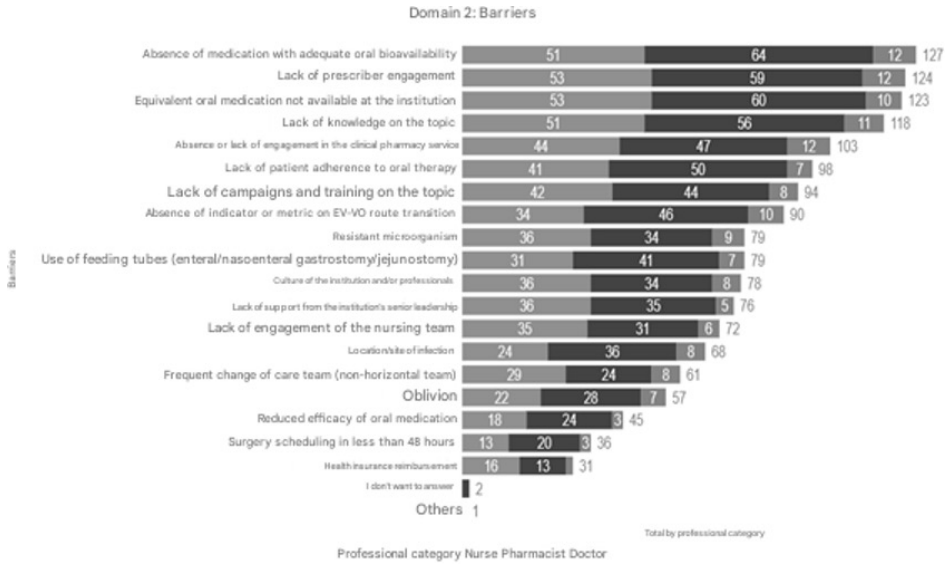

Figure 2. Barriers to transitioning off medication. São Carlos. São Paulo. Brazil, 2022.
Abbreviations: IV/OA: intravenous, oral.

Among the facilitators for TAR, the possibility of hospital discharge was highlighted by 142 (85%) participants, the presence of an active Hospital Infection Control Committee (HICC) was highlighted by 137 (82%) participants, and the cost of oral therapy was highlighted by 136 (81%) participants (Figure 3).

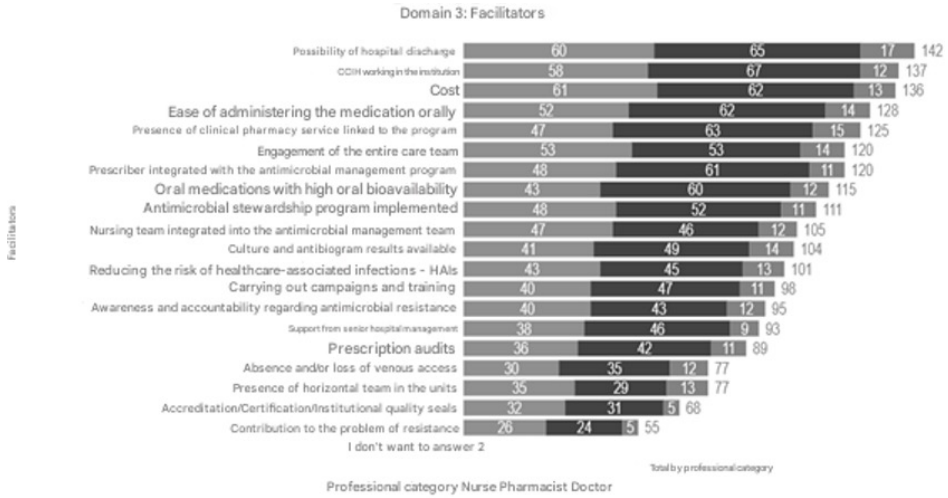

Figure 3. Facilitators for the transition of care. São Carlos. SP. Brazil, 2022.
Abbreviations: HICC: hospital infection control committee.

With regard to the contributions of professionals to TAR, the main contributions of nurses were identified as effective communication with the team about the patient's parameters and condition (86.8%), assessment of the presence of diarrhea, nausea, and vomiting (85.6%), and assessment of the patient's swallowing condition (82.0%). The main contributions of pharmacists were the assessment of the availability of the appropriate oral option for TAR (88.0%), the assessment of the technical aspects of oral antimicrobials (81.4%), and the monitoring of treatment time (73.7%). Finally, the main contributions of the physician were switching the antimicrobial to the oral route in the prescription when appropriate (92.2%), assessing the clinical response to the antimicrobial (85.6%), and assessing the patient's hemodynamic and clinical stability (79.6%).

Finally, with regard to the domain addressing the criteria and parameters for TAR, for more than 85% of the participants, the following criteria and parameters should be considered for TAR: availability of adequate oral medication, patient's willingness to receive oral medication, patient's vital signs, and hemodynamics. On the other hand, participants indicated that they would not recommend TAR in the following situations: suspected gastrointestinal bleeding (79%), critically ill patients (77%), and infection by multidrug-resistant pathogens (66%).

DISCUSSION

Despite Brazil's continental dimensions and regional diversity in relation to the implementation of health policies, and considering that the first version of

ANVISA's guideline for the implementation of ASP in health services was only published in 2017, it is surprising that 64.1% of participants reported having knowledge about ASP.

A Brazilian study evaluated the implementation of PHC in adult intensive care units (ICUs) throughout Brazil, with the significant participation of 954 hospitals, and also presents surprising data, since the findings pointed to the implementation of the program in almost 50% of these institutions.[10]

Considering Primary Health Care (PHC), it is emphasized that more research is needed to investigate this issue. In fact, a Brazilian study conducted only with PHC nurses showed that 74.1% of participants reported no knowledge of the existence of PHC in the municipality where they worked.[11] This fact corroborates the need to also look at PHC for the optimization of antimicrobial use.

PHC is present throughout the national territory and is the main gateway to the Health System, as well as an important link in the continuity of care for hospitalized patients. It is therefore of utmost importance to disseminate the principles of optimizing the use of antimicrobials and ASP in these units.

Regarding the knowledge necessary to work in PHC, topics such as microbial resistance and rational use of antimicrobials were mentioned by 96% of participants, which is consistent with findings in the literature addressing the skills and knowledge necessary for nurses, pharmacists, and physicians working in PHC.[12-13]

Regarding knowledge about TAR, it is concerning that 28% of participants consider that TAR, despite being economical, may lead to worsening of the patient's condition, since oral medications do not have the same potency or efficacy. This position is corroborated by the findings in the literature, where data indicate that professionals mistakenly believe that oral antimicrobials are not as effective as parenteral antimicrobials or are not capable of adequately treating infections.[5,14] These findings reinforce the need to work on specific concepts about antimicrobials, including the pharmacokinetics, pharmacodynamics, and spectrum of action of these drugs.[15]

Considering the barriers to TAR, the absence of drugs with adequate oral bioavailability was the condition most cited by participants (76%). The development of new antimicrobials with good oral availability in recent decades, such as quinolones, cephalosporins, and metronidazole, has enabled a more favorable outlook for TAR, including the challenging scenario of severe gram-positive infections, since the introduction of oral linezolid on the world market.[5]

Even so, the pharmaceutical industry is increasingly challenged to produce new antimicrobials, including oral formulations. However, it should be noted that the list of agents in research or registration phase published by the WHO in 2024 points to 40 items in the investigation or registration phase with oral formulation.[16] Of these, 13 options are intended for priority pathogens, 19 are intended for the treatment of tuberculosis, and nine represent options for non-traditional antibacterial agents.

One possibility to overcome this barrier and, at the same time, bring clarity to the issue associated with the efficacy of oral antimicrobials would be the adoption of institutional protocols for TAR as an activity integrated with PHC, an action considered easy to implement.[17]

The second most cited barrier by participants (76%) in this study points to the lack of engagement by prescribers for the transition to occur. This point highlights the importance of involving and engaging physicians within PHC, as they are the main actors in the prescription of antimicrobials.[18]

The possibility of hospital discharge and the cost associated with IV versus OA antimicrobial therapy were cited by more than 80% of participants as facilitating factors in TAR. In this sense, establishing antibiotic therapy that can bring about the best clinical outcome, with less toxicity and lower cost, are essential principles of ASPs and the object of antimicrobial stewardship.

A recent systematic review conducted to evaluate the effectiveness of interventions related to the IV/OA transition of antimicrobials in hospitals analyzed 36 studies, concluding that all interventions resulted in the optimization of antimicrobial use and reduced healthcare costs without compromising clinical outcomes.[4]

A Brazilian retrospective study evaluated mortality as the primary outcome and costs and length of stay in the ICU as secondary outcomes, concluding that the IV/OA transition is a safe strategy that generates savings and reduces the length of stay in the unit.[19] This reaffirms the facilitating aspects of cost reduction and the possibility of early discharge from the transition of antimicrobial routes.

Knowing the barriers that most impact TAR enables strategies to be developed to overcome these barriers at the institutional level. Similarly, knowing the facilitating elements enables them to be strengthened by health service management. This knowledge has the potential to generate assertive actions that result in a cultural change in the institution regarding TAR. To this end, strengthening the participation and integration of the professionals involved in this topic is essential.

According to this study, the most relevant aspect of the nurse's contribution is effective communication with the team. This finding confirms the role of nurses as a key element in communication with other members of the PHC.[20]

Despite the various activities carried out by nurses within PHC, including TAR, a Brazilian study pointed out that their collaboration with TAR was a practice occasionally performed by these professionals.[21] However, in the present study, assessment of the presence of diarrhea, nausea, vomiting, and swallowing condition were pointed out as contributions of nurses by more than 80% of the participants, reinforcing that nurses already perform several activities related to the optimization of antimicrobial use, but may not be formally included in these programs.

The assessment of the availability of adequate oral options, the technical aspects of oral antimicrobials, and the recording and monitoring of treatment days were pointed out as important contributions of pharmacists. A Japanese study reaffirms this finding, showing that ASP led by a pharmacist specializing in infectious diseases contributes to reducing the duration of antimicrobial treatment.[22]

Promoting the rational use of antimicrobials and guiding other professionals on the technical aspects of medications are pharmaceutical duties that have been strengthened since the development of clinical duties for pharmacists. However, it was only in 2024 that the Federal Pharmacy Council (CFF) regulated the duties of pharmacists in the control of ARIs and the management of antimicrobials.[23]

Infectious disease physicians play an important role in the hospital and PHC settings, not only because they work directly with concepts and tools of epidemiology and infection control, alongside infection control nurses, but also because they actively participate in and often lead PHC teams, thus acting as coordinators of these actions.

Skills and expertise in microbiology, diagnosis and treatment of infectious diseases, infection control, antimicrobial resistance, and direct work with interdisciplinary teams place infectious disease physicians as facilitators not only among other professionals but also among other clinicians who work in direct patient care, enabling them to engage these professionals.[24]

A German study found that interprofessional collaboration between intensive care physicians, nurses, and pharmacists enabled the optimization of antimicrobial use in the ICU, as well as improved outcomes and patient care, generating significant savings for the institution.[25]

The integration of these professionals enables TAR to occur safely and without negatively impacting the patient's clinical outcome. Therefore, knowing the relevant criteria that make a patient eligible for route transition is a task that enables this intervention to occur safely and effectively.

The criteria most cited by the participants in this study corroborate those found in the literature, such as the availability of adequate oral medication, vital signs, fever spikes, the patient's willingness to receive medication enterally, improvement or stability of infectious screening tests, among others.[5,12,15]

In the current study, more than 90% of participants agree that the patient, to be eligible for TAR, needs to meet specific criteria and conditions. These findings reinforce once again the need for well-designed protocols so that this action can be performed safely and effectively.

With regard to the benefits for nursing, pharmacy, and medicine, and in particular for raising awareness about the impact of microbial resistance and actions within ASPs to address it, this study makes it possible to identify important gaps and opportunities, such as the need to formally integrate nurses into ASPs, the importance of developing the skills and abilities of all professionals involved, as well as the need to strengthen the integration of nurses, pharmacists, and physicians, with a view to implementing and strengthening ASPs.

Considering the various positive aspects of TAR at the right time, this study highlights points of attention for strengthening this strategy as well as barriers to be overcome in order to optimize the use of antimicrobials.

This study identified barriers and facilitators for the transition of antimicrobial routes from the perspective of nurses, pharmacists, and physicians. The main barriers identified were the absence of antimicrobials with adequate oral bioavailability and the lack of engagement of prescribers; and the main facilitators were the possibility of hospital discharge, the presence of an active hospital infection control service, and the lower costs associated with oral therapy.

TAR is an intervention that involves direct actions by nurses, pharmacists, and physicians. The present study identified the main contributions of each of these professionals and highlighted the need for all actors involved in primary care to develop competencies and skills for the effective development of these activities in an integrated manner, with interdisciplinary work. The limitations of this study include the small sample size, with emphasis on the fact that the number of medical professionals who responded to the questionnaire was lower than expected, despite the wide dissemination through the technological resources provided for in the methods and approved by the REC. Thus, these limitations should be considered in the interpretation of the findings, requiring further studies to generalize the results.

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AUTHORS' CONTRIBUTIONS

Tatiane Garcia do Carmo Flausino contributed to the bibliographic research, writing of the abstract, introduction, methodology, discussion, interpretation and description of the results, preparation of tables, conclusions, review, and statistics. **Rosely Moralez de Figueredo** contributed to the bibliographic research, writing of the abstract, introduction, methodology, discussion, interpretation and description of results, preparation of tables, conclusions, review and statistics, and project management. **Darlyani Mariano da Silva** contributed to writing the abstract, methodology, interpretation of results, conclusions, review, and statistics. **Lívia Cristina Scalon da Costa Perinoti** contributed to writing the abstract, methodology, interpretation of results, conclusions, review, and statistics.

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

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Original Article

Spatial analysis of suicide mortality in Espírito Santo state

Análise espacial da mortalidade por suicídio no Espírito Santo
Análisis espacial de la mortalidad por suicidio en el estado de Espírito Santo

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Corresponding author:
E-mail: vhms.martins@gmail.com
Address: Fernando Corrêa da Costa Avenue, No. 2367 – Good Hope, Cuiabá, Mato Grosso, Brazil.

Josilene Dália Alves[1]
Camila da Silva Souza[2]
Bárbara Rodrigues de Medeiros[3]
Marcela Silva Fernandes[3]
Marina Nolli Bittencourt[1]
Victor Hugo Martins Santos[4]
Juliane Macedo Manzini[5]

[1]Federal University of Mato Grosso, Barra do Garças, Mato Grosso, Brazil.
[2]Clinical Hospital of the Ribeirão Preto School of Medicine of the University of São Paulo, Ribeirão Preto, São Paulo, Brazil.
[3]Capixaba Institute of Education, Research and Innovation in Health, Vitória, Espírito Santo, Brazil.
[4]Federal University of Mato Grosso, Cuiabá, Mato Grosso, Brazil.
[5]Pontifical Catholic University of São Paulo (PUC-SP), Psychology: Social Psychology, São Paulo, Brazil.

ABSTRACT

Background and Objectives: Although there are studies on suicide mortality in Espírito Santo, few assess its spatial distribution, especially in regions with different socio-economic and cultural characteristics, which makes it difficult to identify spatial patterns and limits the planning of preventive actions. Therefore, the aim was to analyze the characteristics and spatial pattern of suicide mortality in the state of Espírito Santo between 2011 and 2020. **Methods:** this was an ecological study of suicide deaths recorded in Espírito Santo state. The characteristics of the deaths were analyzed using descriptive statistics. Spatial analysis indicating emerging areas in the state was performed using the spatial distribution of suicide mortality rates and by applying a spatial association analysis technique called the Getis Ord Gi*. **Results:** Between 2011 and 2020, 1,987 deaths by suicide were recorded, with the rate rising from 4.62 to 6.17 deaths per 100,000 inhabitants. Deaths by suicide were more frequent among men (n=1,459), in the 30-39 age group (n=408), and of brown race/color. The most common method used was hanging (n=1,147), followed by autointoxication (n=371). The application of the Getis-Ord Gi* technique revealed hot spots in the following regions: Midwest, Central Serrana (with the exception of Itarana), Metropolitana, Southwest Serrana, Caparaó, Central Sul and Litoral Sul. Cold spots were observed in the north-east and north-west of the state. **Conclusion:** understanding the profile and spatial distribution of cases in Espírito Santo can serve as a guide for priority actions to prevent suicide in the state.

Keywords: *Epidemiology. Suicide. Spatial Analysis.*

RESUMO

Justificativa e Objetivos: Embora existam estudos sobre mortalidade por suicídio no Espírito Santo, poucos avaliam sua distribuição espacial, principalmente em regiões com características socioeconômicas e culturais distintas, o que dificulta a identificação de padrões espaciais e limita o planejamento de ações preventivas. Assim, objetivou-se analisar as características e o padrão espacial da mortalidade por suicídio no estado do Espírito Santo no período entre 2011 e 2020. **Métodos:** Estudo ecológico que avaliou óbitos por suicídio registrados no Espírito Santo. As características dos óbitos foram analisadas por estatística descritiva. A análise espacial indicando áreas emergentes no estado foi realizada com a distribuição espacial das taxas de mortalidade por suicídio e pela análise de associação espacial denominada técnica de Getis-Ord Gi*. **Resultados:** Entre 2011 e 2020 foram registrados 1.987 óbitos por suicídio, com a taxa passando de 4,62 para 6,17 óbitos/100 mil habitantes. Predominaram mortes em homens (n=1.459), na faixa etária de 30-39 anos (n=408), e de raça/cor parda. O método mais utilizado foi o enforcamento (n=1.147), seguido por autointoxicações (n=371). A aplicação da técnica Getis-Ord Gi* revelou *hot spots* nas regiões Centro-Oeste, Central Serrana (exceção Itarana), Metropolitana, Sudoeste Serrana, Caparaó, Central Sul e Litoral Sul. *Cold spots* foram observados no Nordeste e Noroeste do estado. **Conclusão:** A compreensão do perfil e da distribuição espacial dos casos no Espírito Santo pode servir como orientação para ações prioritárias de prevenção do suicídio no estado.

Descritores: *Epidemiologia. Suicídio. Análise Espacial.*

RESUMEN

Justificación y Objetivos: Aunque existen estudios sobre la mortalidad por suicidio en Espírito Santo, pocos analizan su distribución espacial, especialmente en regiones con características socioeconómicas y culturales diversas, lo que dificulta la identificación de patrones espaciales y limita la planificación de acciones preventivas. Por lo tanto, el objetivo fue analizar las características y el patrón de distribución espacial de la mortalidad por suicidio en el estado de Espírito Santo entre 2011 y 2020. **Métodos:** Estudio ecológico que evaluó los suicidios registrados en Espírito Santo. Las características de los fallecimientos se investigaron mediante estadísticas descriptivas. El análisis espacial, que identifica áreas emergentes en el estado, se realizó con la distribución espacial de las tasas de mortalidad por suicidio y mediante la técnica de asociación espacial conocida como Getis-Ord Gi*. **Resultados:** Entre 2011 y 2020, se registraron 1.987 suicidios, con una tasa que aumentó de 4,62 a 6,17 muertes por 100.000 habitantes. Predominaron los hombres (n = 1.459), con edad entre 30 y 39 años (n = 408), y de raza/color pardo. El método más utilizado fue el ahorcamiento (n = 1.147), seguido de autointoxicaciones (n = 371). La técnica Getis-Ord Gi* reveló *hot spots* en las regiones: Centro-Oeste, Serrana Central (excepto Itarana), Metropolitana, Serrana Sudoeste, Caparaó, Central Sur y Litoral Sur. *Cold spots* se observaron en el Nordeste y Noroeste. **Conclusión:** Comprender el perfil y la distribución espacial de los casos en Espírito Santo puede orientar las acciones prioritarias para para la prevención del suicidio en el estado.

Palabras Clave: *Epidemiología. Suicidio. Análisis Espacial.*

INTRODUCTION

Suicide is a complex and multicausal phenomenon that represents a serious public health problem globally. In the year 2019 it was the fourth main cause of death among teenagers and young adults aged 15 to 29 years old; and for each adult that materializes self-inflicted death, at least another 20 attempt to take their own lives.[1] Thus, it is considered a type of violent death with one of the highest incidences in the world. Suicide is a phenomenon with a cascade effect, which affects not only the individuals, but also their families, communities and the society as a whole. It is related to risk factors that include those of sociologic, economic, political nature, passing through psychological and psychopathological, biological and the barriers to the access to healthcare.

Besides that, other factors are cited: social inequality, low income, unemployment, schooling, gender, age, previous suicide attempts – which predispose to a progressive lethality of the method – mental health issues, licit or illicit drug use, lack of social support, family history of suicide, strong suicide will, and stressing events.[2] Therefore, although this is a phenomenon that occurs globally, considering the social and economic factors, 77% of the suicide cases were concentrated in low- and middle-income countries in 2019.[1]

Despite the global mortality by suicide has declined 36% between 2000 and 2019, data show that the Americas was the only region where the rate increased in that period, reaching nine deaths per 100,000 population in 2019. In the region, Brazil is the country with the second highest absolute number of deaths by suicide, presenting 14,540 deaths in the year 2019, behind only the United States.[1]

Brazil is also among the 10 countries with the highest number of suicides in the whole world, being the Southern, Midwestern and Northern regions the ones presenting the highest mortality rates by this cause. From 2010 to 2019, there was an increase of 43% in the yearly number of deaths by suicide in the country, and the analysis of the adjusted mortality rates in this period showed an increase in the risk of death by suicide in all regions of Brazil.[3]

However, the country still faces a scarcity in governmental programs that effectively work with suicide prevention, and this situation gets even more overwhelming when we consider the heterogeneity of the phenomenon in the different regions of the country, highlighting the importance of not only think of national public policies, but also regional/local policies that encompass the singularities of each region.[4]

In the Southeastern region, the states of Minas Gerais and Espírito Santo are at the top of the rank of death rates by suicide, and reported 8.2 and 6.5 deaths per 100,000 population, respectively, in the year 2019.[3] From 2003 to 2016, the mortality rate by suicide presented stability, ranging from 3.9 to 4.4 deaths per 100,000 population. From 2017, the number of deaths increases and ranges from 5.2 to 5.82 in the years 2017 and 2018.[5] On the other hand, a study by Tavares and collaborators6 shows that the mortality rate by self-inflicted injuries in the year 2016 was 6.2 per 100,000 population, with an increase of 30.3% in the deaths by suicide during the period from 2012 to 2016.

When we analyzed the victims' sociodemographic profile, we noticed that most of the cases are adult males and point to the difference between male and female when it comes to methods used. Among male, hanging was the most prevalent method, while among female poisoning and jumping from a height were more common. As for the region, from 2018, we observed an increase in the mortality rates in the Greater Vitória Metropolitan Region (Região Metropolitana da Grande Vitória/RMGV).[6]

Given this scenario, it is important to emphasize the need for investments in research that increases the availability of information regarding the population's health situation and for the planning of actions targeting the prevention of suicide, and interventions in risk areas and vulnerable populations, aiming to modify the impact of this phenomenon and the mortality in the future. Considering this situation, spatial analysis is an important tool to perform the situational diagnosis of a region, enabling the assessment of results according to the socioeconomic, cultural and environmental reality.[7]

It is noteworthy that, although there are studies addressing the mortality by suicide in Espírito Santo state, studies using spatial analysis methods are scarce, mainly in regions with distinct socioeconomic and cultural characteristics. If there is no understanding of how this phenomenon is distributed in space, it is not possible to direct the actions to vulnerable groups and areas, making suicide prevention actions ineffective. In light of this, the present study has the objective of analysing the characteristics and the spatial distribution pattern of mortality by suicide in the state of Espírito Santo from 2011 to 2020. We expect that the data generated will contribute to the planning, consolidation and assessment of health policies, as well as the strengthening of actions in mental health.

METHODS

Study Type

Ecological study assessing deaths due to suicide reported in Espírito Santo state from 2011 to 2020. The study period was chosen taking into consideration the possibility of analyzing the phenomenon broadly during a decade of important social and technological changes.

Study Location

With Regard to the study setting, the state of Espírito Santo is situated in the Southeastern region of Brazil, with a residing population of 3,833,486 people in 2022. It is the 14th largest State population in the country, with a territory of 46,074.448 km² and demographic density of 83.21 people/km², divided in 78 municipalities. In this context, Espírito Santo state has a Human Development Index (HDI) of 0.771; the municipalities with the highest HDI are Vitória (0.845) and Vila Velha (0.800), while Santa Leopoldina (0.626) and Ibitirama (0.622) present the lowest HDI, values considered as a medium HDI.[8-9]

Among the main cities in the state is the capital Vitória, as well as the municipalities of Vila Velha, Serra, Cariacica, Guarapari, Fundão and Viana, which are part of the Greater Vitória Metropolitan Region. Besides the Metropolitan Region, it is importante to point out the municipalities of Cachoeiro de Itapemirim, Linhares, São Mateus, Colatina and Aracruz.

The Greater Vitória Metropolitan Region has the highest percentage (49.1%) of urbanization of the state.[9] As for the health regions, the regional boundaries that established in the territory of Espírito Santo state three Health Regions (Central/North, Metropolitan and South), serving as an organizational foundation for the health sector, were approved through the Resolution 153/2020 of the Bipartite Inter-managerial Committee (CIB/SUS-ES), in December 18th, 2020.[10] According to this document, the Metropolitan health region covers the largest population, the equivalent to 2,410,051 people in the year 2020, corresponding to more than half of the state's population.

In light of this, only deaths resulting from intentionally self-inflicted injuries, as classified in Chapter XX of the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10), were selected and tabulated by ICD-10 category according to the codes for each injury (X60–X84).[11]

Data on suicide deaths were obtained from death certificates registered in the Mortality Information System (SIM) of the Department of Informatics of the Unified Health System (DATASUS) of the Ministry of Health. Data collection was conducted between March and April 2023.

The population data by municipality, for each year of the study, used to calculate the mortality rate, were obtained from the mid-year population estimates calculated by the Brazilian Institute of Geography and Statistics (IBGE) and provided to the Federal Court of Accounts (TCU).

Data Analysis

In the first stage, the exploratory data analysis covered the dimensions of sociodemographic characteristics (gender, age, race/color, marital status, education level, occupation). In accordance with this information, the items were evaluated for consistency and completeness, followed by descriptive analysis, with calculation of absolute and relative frequencies using SPSS software, version 29.0.

In the second stage, a spatial analysis of suicide deaths was conducted in Espírito Santo. For this purpose, suicide mortality rates were calculated for each municipality in the state of Espírito Santo, according to the study period. The calculation was performed by dividing the total number of notified deaths by the standard population (the mid-period study population) for each municipality, then multiplying the result by 100,000, and finally dividing by 10, which corresponds to the number of years covered in the study (2011–2020).

In the next step, the spatial distribution of suicide mortality rates was carried out across the municipalities of Espírito Santo by creating thematic maps using ArcGIS version 10.8.1. This software is specifically designed for the creation, management, sharing, and analysis of spatial data. In the maps, the darker colors represent municipalities with the highest suicide mortality rates.

In the spatial association analysis, the Getis Ord Gi* technique (pronounced 'G i star') was used. This Gi* statistic, developed by Getis and Ord, is an indicator of local spatial association.[12] The GI* index is based on analyzing the sum of neighboring values, defined using a neighborhood matrix Wij.[12] For defining the neighborhood, a fixed distance was adopted, defined as the average distance between municipalities, because it allows capturing local clusters without depending on the demographic density of each region. The critical distance was 30 km, which allows the identification of regional patterns. For the spatial weights matrix, the inverse distance matrix was determined, which preserves local influence without dispersing patterns. The FDR (False Discovery Rate) method was applied to reduce the occurrence of false positives and preserve the ability to detect real clusters. The Gi* statistic indicates the extent to which a location is surrounded by a cluster (aggregation) of high values (hot spot) or low values (cold spot) of the analyzed variable. The interpretation of this statistic is based on the sign of Z (z score) and the values of the significance level (α). A positive and significant z-value for the statistics indicates spatial clustering of high values, while a negative and significant z-value indicates spatial clustering of low values.

Ethical aspects

This research used secondary data obtained from a public domain database, with no subject identification, provided by the Ministry of Health website. Therefore,

it is exempt from review by an ethics committee, in accordance with Resolution No. 510 of 2016 of the Brazilian National Health Council.

RESULTS

From 2011 to 2020, according to the Mortality Information System (SIM) data, 1,987 suicide deaths were recorded in the state of Espírito Santo. According to SIM data, the mortality rate varied from 4.62 deaths per 10,000 population in 2011 to 6.17 deaths per 100,000 population in 2020 (Table 1).

Table 1. Number of deaths and suicide mortality rates by study year, Espírito Santo, Brazil, 2011–2020.

Year	No Deaths by Suicide	RT/100,000 pop
2011	164	4.62
2012	177	4.95
2013	159	4.14
2014	173	4.45
2015	189	4.81
2016	175	4.40
2017	208	5.18
2018	239	6.02
2019	252	6.27
2020	251	6.17

Abbreviations: **RT=number of deaths.*

Of the total deaths, 73.4% (n = 1,459) occurred in the male population, and 26.52% (n = 527) in the female population. Regarding age, deaths occurred most frequently (23.05%) in the 30–39 years age group (n = 408), followed by the 40–49 years age group (n = 451; 22.69%). Individuals self-identified as mixed-race (brown) accounted for the highest number of suicide deaths in Espírito Santo during the study period (n = 1,080; 54.35%) (Table 2).

Table 2. Sociodemographic characteristics of suicide deaths, Espírito Santo, Brazil, 2011–2020, n = 1,987.

Variables	N (%)
Sex	
Female	527 (26.52)
Male	1459 (73.43)
Unknown	1 (0.05)
Age group	
10-14 years	16 (0.81)
15-19 years	99 (4.98)
20-29 years	362 (18.22)
30-39 years	458 (23.05)
40-49 years	451 (22.69)
50-59 years	317 (15.95)
> 60 years	284 (14.30)
Race	
Mixed (brown)	1080 (54.35)
White	646 (32.51)
Black	111 (5.59)
Indigenous	1 (0.05)
Yellow (Asian)	1 (0.05)
Unknown	148 (7.45)
Level of education	
No education	47 (2.37)
1 to 7 years	507 (25.51)
8 to 11 years	295 (14.85)
12 years or more	134 (6.74)
Unknown	1004 (50.53)
Marital Status	
Single	794 (39.96)
Married	591 (29.74)
Legally separated	54 (2.72)
Widowed	157 (7.90)
Other	64 (3.22)
Unknown	327 (16.46)

Regarding the method used to complete suicide, more than half of the deaths were by hanging (n = 1,147; 57.7%), followed by self-intoxication (n = 371; 18.7%), which refers to the act of ingesting medication on one's own (Table 3).

Table 3. Suicide deaths by type of self harm according to ICD 10 category and place of occurrence, Espírito Santo, Brazil, 2011–2020.

Variables	N (%)
CID-10 Category	
Self-intoxication	371 (18.67)
Hanging	1147 (57.72)
Drowning	29 (1.46)
Firearms	143 (7.20)
Smoke/fire/flames	51 (2.57)
Steam/water/gas/hot object	2 (0.10)
Sharp/blunt object	49 (2.47)
Jumping from a height /moving object	133 (6.69)
Impact of a motor vehicle	6 (0.30)
Others	56 (2.82)
Place of occurrence	
Home	1,054 (53.05)
Hospital/other healthcare institutions	472 (23.75)
Public streets	129 (6.49)
Others	313 (15.75)
Unknown	19 (0.96)

In the spatial analysis of suicide, considering the distribution of crude mortality rates for the study period, the municipalities with the highest suicide mortality rates were Afonso Cláudio (12.02 deaths per 100,000 population), Iúna (11.83 deaths per 100,000 population), and Domingos Martins (10.17 deaths per 100,000 population). The municipalities with the lowest mortality rates during the same period were Ibitirama (1.07 deaths per 100,000 population), Pinheiros (1.5 deaths per 100,000 population), and Boa Esperança (1.96 deaths per 100,000 population). The spatial distribution of crude suicide mortality rates from 2011 to 2020 is presented for each municipality in the state (Figure 1).

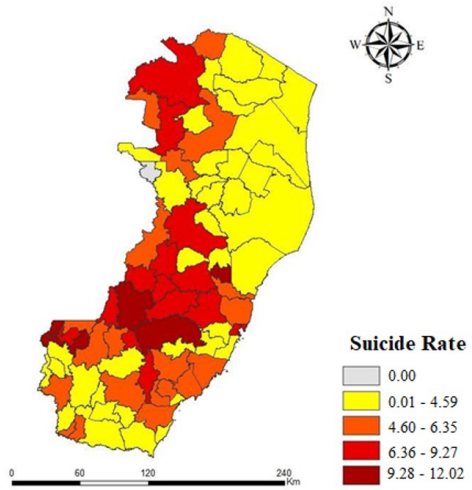

Figure 1. Distribution of suicide mortality rates (per 100,000 population) across municipalities in Espírito Santo, Brazil, 2011–2020.

The results of the local spatial association analysis of suicide rates, using the Getis-Ord Gi* technique, enabled the identification of areas with high occurrence (hot spots) and low occurrence (cold spots) of cases and their distribution during the study period (Figure 2).

Between 2011 and 2020, clusters of higher suicide occurrence were observed in municipalities from the following regions: Central-West of the state (Baixo Guandu and São Roque do Canaã), Central Serrana (except Itarana), Metropolitan, Southwest Serrana, Caparaó, Central South, and South Coast of the state. The presence of clusters with lower occurrence (cold spots) was concentrated in the Northeast and Northwest regions, including the municipalities of Sooretama (Rio Doce region), Vila Valério, and São Gabriel da Palha (Central-West). The results found indicated a spatial association with suicide deaths in the state of Espírito Santo.

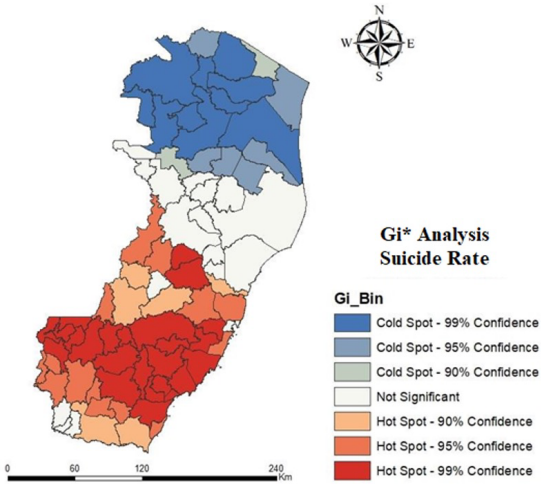

Figure 2. Clusters of high and low suicide mortality rates, distributed across municipalities in Espírito Santo, Brazil – 2011–2020.

DISCUSSION

In Espírito Santo, the highest percentages of suicide deaths have been reported among males, individuals aged 30–39, and those of mixed-race descent. Considering the distribution of the mortality rate, it was observed that between 2011 and 2020, the highest number of suicide deaths occurred outside the Metropolitan Region.

A previous study indicated a growing trend in suicide rates in the Metropolitan, Northwest, and South regions of Espírito Santo state. This difference in the higher number of deaths found outside the Metropolitan Region can be justified, considering the increased identification and classification of suicide as a cause of death, due to the expanded coverage of the Mortality Information System (SIM), as well as the correct completion of death certificates, despite still being a process where underreporting occurs.[6]

An analysis of death records by gender revealed a significantly higher incidence of suicide among men compared to women. In much of the world, including Brazil, suicide deaths also predominantly affect the male population.[13] According to the Ministry of Health's Epidemiological Bulletin (2021),3 the risk of death by suicide among men is 3.8 times higher than among women, a finding consistent with studies conducted in different regions of the country. In addition to the choice of more lethal methods, several hypotheses explain the higher suicide rates among men, such as increased consumption of drugs and alcohol, impulsive behaviors, and greater sensitivity to financial instability, including unemployment and poverty.[14] In relation to the female population, maternity and pregnancy are considered protective factors due to the care that will be provided to the child. Additionally, it can be said that the search for professionals for early diagnosis and treatment of mental health issues is more common compared to men, a situation that may explain the lower suicide rate among women.[14]

Although suicide is predominantly male, an increase in suicide rates among women has been observed, as evidenced by research indicating growth between 2007 and 2016.[14-15] These findings reveal that, although suicide mortality among women is lower than among men, it is an increasing event.

Regarding race/color, in general, the mixed-race (brown) population was the most affected, followed by the white population. These findings align with the results of the latest IBGE Census, which indicated that the majority of the state's population is mixed-race.[9] As for the race/color category, there is a noticeable difficulty among professionals in completing declarations in this regard, with completion rates ranging from 3% to 25%. Nevertheless, there has been an improvement in the completion percentages.[15]

The variable 'education level' presents a high number of ignored cases, which was also found in previous studies.[16] The data obtained showed a higher number of deaths among individuals with four to seven years of schooling, that is, those who had completed up to the first stage of elementary education. Similar findings have been observed in other parts of the world, indicating that low education is a risk factor for suicide.[17-18]

Regarding the most commonly used methods, hanging followed by self-poisoning remained the leading causes of suicide, and there is consensus in the literature that hanging is the most frequently used method.[15] Hanging does not require the acquisition of a specific tool, which facilitates the suicidal act, making it more difficult to control access. Therefore, the early identification of individuals at risk is crucial for implementing measures that limit access to this means.[16]

Regarding age, the most affected age groups were 30–39 and 40–49 years, indicating that older individuals, especially males, committed more suicides. This finding aligns with American epidemiological studies, which reported an increase in suicide rates within this age group.[19] A systematic review on suicide and suicide

attempts in adults pointed out that various factors are involved in these cases, such as recent adverse events, a history of mental disorders, and self-harm.[20]

It is important to emphasize that various individual and social factors are involved in the array of risk factors related to suicide, including age and adverse life experiences, as well as variables pertinent to each stage of life. Therefore, it is essential that preventive measures be planned not only individually but also collectively, taking into account the specific risk factors of each region.[18]

This leads the World Health Organization to consider suicide a global public health issue, as it has psychosocial and economic impacts.[1] These include diminished personal capacity, loss of interest and pleasure in daily activities, absenteeism from work, and a decline in the quality of life for both the individual and their family members. This impact is underscored by the increasing economic costs associated with mental disorders, including suicide and suicide attempts, which have been rising each year.[21] Therefore, the phenomenon of suicide, in addition to being a serious health problem, can also represent a significant economic, social, and political challenge. This implies that prevention should not be addressed solely through pharmacological or psychotherapeutic methods; it is essential to involve the community by providing social support to vulnerable individuals, as well as to the families and friends of suicide victims.

Regarding the state's microregional situation, the Metropolitan Region recorded lower suicide rates compared to other regions. This can be attributed to certain areas having better overall living conditions. In the case of the Metropolitan Region, the availability of services and goods, along with better access to employment, transportation, and improved quality of life, can directly contribute to this outcome.

On the other hand, areas facing economic vulnerability tend to have higher suicide rates, as social inequality can foster feelings of injustice, tension, anger, and personal failure due to the inability to achieve economic success. Additionally, the stress from ongoing financial difficulties and anxiety, the lack of success in the search for a job, can lead a person to suffering that may develop into suicidal thoughts or giving up on life. Thus, individuals tend to experience less depression and stress when economic activity is expanding. Therefore, more developed regions may exhibit lower suicide rates.[22]

Finally, it is worth noting that the population living in the mountainous region represents Pomeranian culture, and the self-inflicted violence among this population can be attributed to their hostile, closed-off, and distrustful profile. These factors predispose them to depression and can be exacerbated by excessive alcohol use. This is a population with few leisure options, beyond a life focused solely on rural work - elements that can be considered risk factors for suicide. In other words, the combination of sociocultural and economic variables that have historically been associated with an increased incidence of self directed violence.[23]

Supporting these analyses, a specific study indicated that, between 2001 and 2007, there was a trend of increasing self inflicted violence among the Pomeranian population in the state of Espírito Santo. Data such as age, profession, day of the week, time period of incidents, sex, methods used, and motivation for the act were identified to characterize the profile, considering suicide attempts and mortality. Furthermore, the study highlighted that sociodemographic and cultural factors were related to patterns of this type of death, with the predominance of rural activities, associated with low employability and precarious work, as well as the influence of Protestant religion and the strong value placed on marriage within the population.[24] In this regard, the results obtained point to the need for preventive strategies through the development of public policies aligned with the local reality, especially for the most vulnerable groups.

Spatial analyses conducted in international settings, such as in Australia, highlight the importance of identifying geographic and cultural patterns associated with suicide, contributing to the understanding and prevention of this phenomenon across different populations.[25]

In addition to the ecological design, one of the main limitations of this study concerns the use of data from the Mortality Information System (SIM). Underreporting is a frequent problem in suicide statistics, especially in rural areas or regions further from urban centers where access to health services is limited. In this context, many suicide deaths may be recorded under ill-defined or neglected causes due to the lack of accurate diagnosis or inadequate reporting. The lack of proper records can lead to an underestimation of mortality rates, which can distort the analysis of the population's health patterns and impact data quality due to variability in how deaths are notified.

Furthermore, the use of population estimates to calculate mortality rates, which, although based on censuses and projections, may not accurately reflect the actual population during the study period due to migration and changes in the characteristics of the population.

In the state of Espírito Santo, spatial association analysis indicated that the areas with the highest incidence of suicide are located in the regions Central-West, Central Serrana, Metropolitan, Southwest Serrana, Caparaó, Central South, and South Coast, pointing that suicide occurs heterogeneously in the state.

These results can guide interventions aimed at those territories, with actions to promote mental health and

prevent suicide in priority areas, which may impact mortality indicators in the future.

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AUTHORS' CONTRIBUTIONS

Josilene Dália Alves contributed to the bibliographic research, writing of the abstract, introduction, methodology, discussion, interpretation and description of results, table preparation, conclusions, review, and statistics. **Camila da Silva Souza** contributed to the bibliographic research, writing of the abstract, introduction, methodology, discussion, interpretation and description of results, table preparation, conclusions, review, and statistics. **Marcela Silva Fernandes** contributed to the bibliographic research, writing of the abstract, introduction, methodology, discussion, interpretation

and description of results, table preparation, conclusions, review, and statistics. **Bárbara Rodrigues de Medeiros** contributed to the bibliographic research, writing of the abstract, introduction, methodology, discussion, interpretation and description of results, table preparation, conclusions, review, and statistics. **Marina Nolli Bittencourt** contributed to the writing of the discussion, conclusion, and review. **Victor Hugo Martins Santos** contributed to the writing of the abstract, discussion, and review. **Juliane Macedo Manzini** contributed to project management, bibliographic research, writing of the abstract, introduction, methodology, discussion, interpretation and description of results, conclusions, review, and statistics.

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

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Original Article

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Corresponding author:
E-mail: leticia@ufr.edu.br
Address: Students Avenue, 5055 - University City, Rondonópolis, Mato Grosso, Brazil.

Letícia Silveira Goulart[1]
Ingryd Rodrigues Xavier Docusse[1]
Giulia Elena Tessaro[1]
Ricardo Alves Olinda[2]
Magda de Mattos[1]

[1]Federal University of Rondonopolis, Rondonopolis, Mato Grosso, Brazil.
[2]State University of Paraíba, Campina Grande, Paraíba, Brazil.

ABSTRACT

Background and Objectives: Covid-19 represents a global health problem with high rates of morbidity and mortality and impact on health systems. The objective was to analyze the profile and factors associated with Covid-19 self-report in the context of Primary Health Care. **Methods:** This is a cross-sectional, observational study carried out with users of the Family Health Strategy in the city of Rondonópolis-MT. Data were collected at health units through a semi-structured questionnaire. **Results:** Among the 400 survey participants, 77 (19.25%) reported a diagnosis of Covid-19. The variables associated with the disease self-report were higher income, having health insurance and being in the labor market. The main clinical symptoms were myalgia, fever and headache. Mild cases of the disease predominated and the sentinel unit was the main health service used. **Conclusion:** The data point to the impact of social variables on the diagnosis of Covid-19 and reveal the importance of the services offered by the SUS in the context of the pandemic.

Keywords: *Covid-19. Primary Health Care. Epidemiology. Associated factors.*

RESUMO

Justificativa e Objetivos: A Covid-19 representa um problema de saúde mundial com elevados índices de morbimortalidade e impacto nos sistemas de saúde. O objetivo desta pesquisa foi analisar o perfil e os fatores associados ao autorrelato de Covid-19 no âmbito da Atenção Primária à Saúde. **Métodos:** Trata-se de um estudo transversal, observacional, realizado com usuários da Estratégia Saúde da Família (ESF) do Município de Rondonópolis-MT. Os dados foram coletados nas unidades de saúde por meio de um questionário semiestruturado. **Resultados:** Dos 400 participantes da pesquisa, 77 (19,25%) relataram diagnóstico de Covid-19. As variáveis associadas ao autorrelato da doença foram: maior renda, ter plano de saúde e estar inserido no mercado de trabalho. Os principais sintomas clínicos foram: mialgia, febre e cefaleia. Predominaram os casos leves da doença, e a unidade sentinela foi o principal serviço de saúde utilizado. **Conclusão:** Os dados apontam para o impacto das variáveis sociais no diagnóstico da Covid-19 e revelam a importância dos serviços ofertados pelo Sistema Único de Saúde (SUS) no contexto da pandemia.

Descritores: *Covid-19. Atenção Primária à Saúde. Epidemiologia. Fatores associados.*

RESUMEN

Justificación y Objetivos: El Covid-19 representa un problema de salud mundial con altas tasas de morbimortalidad e impacto en los sistemas de salud. El objetivo fue analizar el perfil y los factores asociados con lo autoinforme de Covid-19 en el contexto de la Atención Primaria de Salud. **Métodos:** Se trata de un estudio transversal, observacional, realizado con usuarias de la Estrategia Salud de la Familia en el municipio de Rondonópolis-MT. Los datos fueron recolectados en las unidades de salud a través de un cuestionario semiestructurado. **Resultados:** Entre los 400 participantes de la encuesta, 77 (19,25%) informaron un diagnóstico de Covid-19. Las variables asociadas con lo autoinforme enfermedad fueron mayores ingresos, tener seguro de salud y estar en el mercado laboral. Los principales síntomas clínicos fueron mialgias, fiebre y cefalea. Predominaron los casos leves de la enfermedad y la unidad centinela fue el principal servicio de salud utilizado. **Conclusión:** Los datos apuntan al impacto de las variables sociales en el diagnóstico de la Covid-19 y revelan la importancia de los servicios ofrecidos por el SUS en el contexto de la pandemia.

Palabras Clave: *Covid-19. Atención Primaria de Salud. Epidemiologia. Factores asociados.*

INTRODUCTION

The disease caused by the new coronavirus, known as Covid-19, was first reported in Brazil in February 2020. In September of that year, the second phase of the pandemic began. However, the highest peak in daily cases and deaths was observed during the third phase, which started in February 2021. From July 2021 onward, with the expansion of vaccination efforts, a decline in the number of infections and deaths was noted, marking the fourth phase, which lasted until November 2021. At that point, infection rates rose once again, characterizing the fifth phase of the pandemic.[1]

The municipality of Rondonópolis, located southeast of Mato Grosso State, presented a distribution pattern of Covid-19 cases throughout the pandemic similar to the national epidemiological trend.[2] For better disease control, measures such as social distancing, mandatory use of masks, and vaccination—initiated in January 2021—were implemented.[3,4]

Covid-19 has several clinical characteristics, ranging from asymptomatic cases to mild, moderate, or severe illness. The most common symptoms are fever, cough, dyspnea, myalgia, and fatigue.[5,6] According to the literature, factors associated with coronavirus infection include advanced age, male sex, Black skin-color, working in healthcare, pre-existing comorbidities, etc.[7-9]

Notably, the dynamics of this disease vary across different regions of Brazil, depending on intra-urban factors such as infrastructure, population density, mobility patterns, and adherence to prevention measures. Urban demographic and socioeconomic conditions can therefore increase the vulnerability of cities and regions to pandemics.[10] Additionally, factors such as the structure, practices, and routines of local health services must also be considered.[11] Primary Health Care services (PHC) played a decisive role during the pandemic by leveraging territorial knowledge, ensuring access, fostering bonds between users and healthcare teams, providing comprehensive care, monitoring vulnerable families, and following up on suspected and mild cases. To ensure quality care at this level, data-informed planning, service reorganization, reallocation of financial resources, and the adoption of specific strategies to confront the pandemic are essential.[12]

Given Brazil's large dimensions and highly diverse local contexts, the country faced challenging pandemic response efforts. Thus, it is important to know and evaluate local epidemiological data to support decision-making.[11] Understanding the dynamics of the Covid-19 pandemic within PHC is crucial to develop measures and policies aimed at reducing health impacts during emergency situations. In this context, this study aimed to analyze the profile and factors associated with self-reported Covid-19 diagnosis within PHC.

METHODS

This is a cross-sectional study conducted with users of the Family Health Strategy (FHS) in the municipality of Rondonópolis, Mato Grosso, from January to September 2021. According to the last census by the Brazilian Institute of Geography and Statistics (IBGE), Rondonópolis—located southeast of Mato Grosso State—has approximately 138,326 residents aged 18 years or older, representing 70.76% of the total population.[13] PHC covers 72.75% of its territory.

The sample size was calculated based on the number of residents aged 18 or older in the municipality, as reported by IBGE. The assumptions used for calculation included a 95% confidence level, a 5% margin of error, and an expected proportion of 0.50. The margin of error refers to the maximum expected deviation of the study results based on the selected sample. The confidence interval represents the probability that the results would be similar if the study were conducted with another group of individuals sharing the same profile, within the same margin of error. This resulted in a sample of 384 users; however, to account for potential losses, 400 individuals were included in the study. A convenience sampling method was used, and participants were selected among users who were present at basic health units at the time of data collection. Although convenience sampling may introduce bias, it was chosen because it is an accessible method for researchers to contact FHS users. Given that data collection took place during the pandemic, visiting participants at home after random selection could have caused discomfort and led to a high number of refusals.

All FHS units located in the urban area of the municipality were included, except those that had been converted into Sentinel Health Units or were closed to the public due to renovations, totaling 40 FHS. During the pandemic, many health units in Rondonópolis were converted into Sentinel Health Units, which aimed to diagnose cases of flu-like syndromes and, therefore, were not limited to serving only the population of the FHS assigned area. Convenience sampling was used, with 10 users selected from each FHS unit, resulting in 400 participants.

Users aged 18 or older were included. Individuals with cognitive impairments or with health conditions that prevented data collection were excluded. Users who met the inclusion criteria were invited to participate in the study and were informed about its objectives; those who agreed to participate signed an informed consent form.

Data were collected from January to September 2021 in a private setting within the basic health units. To ensure standardization in data collection, researchers were trained on how to approach participants and record information on the form. A pilot study was conducted to

adjust the data collection instrument with individuals who were not part of the sample. A semi-structured questionnaire was elaborated using Google Forms, consisting of three sections including question on sociodemographic, clinical, and health service use. The responses were entered directly by the interviewers into the digital platform, and the data were automatically exported into a Microsoft Excel spreadsheet.

To determine factors associated with self-reported Covid-19 diagnosis, the dependent variable in the study was the self-report of a positive laboratory test result for SARS-CoV-2, and the response was dichotomized as "yes" and "no." To assess this, participants were asked: *Have you had a laboratory test that confirmed a Covid-19 diagnosis?*

The following variables were considered as independent variables:

a) Demographic characteristics: sex, age in years, self-reported skin-color, and marital status.

b) Socioeconomic characteristics: schooling in years, household income, number of people living in the household, employment status, whether the individual worked in an essential activity during the pandemic, number of household members who left home due to work, and private health insurance plan.

c) Clinical characteristics: presence of comorbidities and number of comorbidities.

Bivariate logistic regression models were constructed, meaning that each model included only one independent variable in relation to the outcome variable (dependent variable). Adjusted odds ratios (ORs) with their respective confidence intervals (95%CI) were estimated for each bivariate logistic model. The likelihood ratio test was used to verify the significance of the estimated model. Moreover, the Wald test was applied to determine the significance of the model coefficients adjusted to the data. To evaluate the adequacy of the proposed statistical model in describing the observations, the normality and independence of the errors were verified. These procedures aimed to ensure the theoretical assumptions necessary for conducting statistical analyses using univariate techniques. All analyses were performed using the R© programming language, version 3.4.3, and a 5% significance level was set.

The study was approved by the Research Ethics Committee of the Júlio Muller University Hospital, Federal University of Mato Grosso CAEE 39427420.1.0000.5541, approval No. 4,418,798, on November 24, 2020. All ethical principles regarding research involving humans were respected, in accordance with Resolution No. 466/2012.

RESULTS

Of the study participants, 77 reported a laboratory diagnosis of Covid-19, corresponding to 19.25% of the studied population. The average age of users with a history of SARS-Cov-2 infection was 41.78 years. Among participants who self-reported Covid-19 diagnosis, most were male; aged 18–39 years; Mixed-race individuals; living with a partner; five to eight years of schooling; household income of two or more minimum wages, and up to three members in the household. A higher probability of self-reported laboratory Covid-19 diagnosis was also identified among individuals engaged in formal or informal work; those who worked in essential services during the pandemic; individuals living in households where two or more people had to leave home for work; and those with private health insurance (Table 1).

Regarding clinical characteristics, a higher prevalence of self-reported Covid-19 was observed in individuals with comorbidities and among those with two or more comorbidities. A statistically significant difference was found for the variables "engaging in formal or informal work" (p=0.02) and "having a private health insurance" (p<0.01) (Table 1).

Table 1. Profile of the study participants, according to self-reported laboratory Covid-19 diagnosis. Rondonópolis, Mato Grosso. 2021. n=400.

Parameter	Self-reported Covid-19		p-value
	No N (%)	Yes N (%)	
Total	**323 (80.75)**	**77 (19.25)**	
Sex			
Female	231 (81.9)	51 (18.1)	0.43
Male	92 (78.0)	26 (22.0)	
Age in years			
18–39	142 (78.5)	39 (21.5)	0.50
40–59	129 (81.1)	30 (18.9)	
60 or older	49 (86.0)	8 (14.0)	
Self-reported skin-color			
White	79 (79.8)	20 (20.2)	0.61
Mixed-race	177 (79.4)	46 (20.6)	
Black, Indigenous, and Asian	66 (85.7)	11 (14.3)	
Marital status			
No partner	168 (82.4)	36 (17.6)	0.48
With a partner	155 (79.1)	41 (20.9)	

Parameter	Self-reported Covid-19 No N (%)	Yes N (%)	p-value
Years of schooling			
≤ 5	102 (85.7)	17 (14.3)	0.26
6 to 8	18 (78.3)	5 (21.7)	
≥ 9	203 (78.7)	55 (21.3)	
Household income			
Up to one minimum wage	136 (86.1)	22 (13.9)	0.06
Two or more minimum wages	185 (77.1)	55 (22.9)	
Number of household members			
Up to three	215 (80.2)	53 (19.8)	0.80
Four or more	108 (81.8)	24 (18.2)	
Employment status			
Retired	41 (83.7)	8 (16.3)	
Unemployed	140 (86.4)	22 (13.6)	0.02
Formal or informal work	142 (75.1)	47 (24.9)	
Worked in an essential activity during the pandemic			
No	281 (81.2)	65 (18.8)	0.68
Yes	42 (77.8)	12 (22.2)	
Number of household members who left home for work			
Up to one	199 (83.3)	40 (16.7)	0.15
Two or more	124 (77.0)	37 (23.0)	
Private health insurance			
No	282 (83.4)	56 (16.6)	<0.01
Yes	41 (66.1)	21 (33.9)	
Comorbidity			
Yes	113 (79.6)	29 (20.4)	0.75
No	210 (81.4)	48 (18.6)	
Number of comorbidities			
One	87 (80.6)	21 (19.4)	
Two or more	26 (76.5)	8 (23.5)	0.78
None	210 (81.4)	48 (18.6)	

The results showed that self-reported laboratory Covid-19 diagnosis among FHS users was associated with income (OR: 0.54; 95%CI: 0.32–0.94), employment status (OR: 2.11 (1.21–3.68), and having private health insurance (OR: 0.39; 95%CI: 0.21–0.71). The sociodemographic characteristics "lower income" and "not having a private health insurance" were identified as protective factors against self-reported laboratory Covid-19 diagnosis. However, individuals who engaged in formal or informal work during the pandemic were 2.11 times more likely to report a history of Covid-19 (Table 2).

Table 2. Bivariate analysis of Primary Health Care users' characteristics according to self-reported laboratory Covid-19 diagnosis. Rondonópolis, Mato Grosso. 2021. n=400.

Parameter	OR (95%CI)	p-value
Sex		
Male	1.28 (0.75–2.18)	0.36
Female	1	
Age group in years		
18–39	1	
40–59	0.85 (0.5–1.44)	0.54
60 or older	0.59 (0.26–1.36)	0.21
Marital status		
No partner	1	
With partner	1.23 (0.75–2.03)	0.40
Years of schooling		
≤ 5	0.62 (0.34–1.11)	0.10
6 to 8	1.03 (0.36–2.89)	0.96
≥ 9	1	
Monthly family income		
Up to one minimum wage	0.54 (0.32–0.94)	0.02
Two or more minimum wages	1	
Employment status		
Retired	1.24 (0.51–3.00)	0.63
Formal or informal work	2.11 (1.21–3.68)	0.009
Unemployed	1	
Worked in an essential activity during the pandemic		
No	1	
Yes	1.24 (0.62–2.48)	0.55
How many people left home for work		
Up to one	1	
Two or more	1.48 (0.9–2.45)	0.12
Private health insurance		
No	0.39 (0.21–0.71)	<0.01
Yes	1	

Parameter	OR (95%CI)	p-value
Comorbidity		
Yes	1.12 (0.67–1.88)	0.65
No	1	
Number of comorbidities		
One	1	
Two or more	1.27 (0.51–3.21)	0.60

Abbreviations: OR: Odds Ratios; 95%CI: 95% confidence interval.

Most research participants who reported having received a Covid-19 diagnosis self-reported their health status as good (50.65%) and had no comorbidities (62.34%). The most commonly used diagnostic method was RT-PCR (48.05%), performed mainly at sentinel health units (59.74%). Over half of users (59.74%) did not receive follow-up care from the basic health unit, 93.51% were not hospitalized, and no patients were admitted to an Intensive Care Unit (Table 3).

Table 3. Clinical characteristics of Primary Health Care users with self-reported laboratory Covid-19 diagnosis. Rondonópolis, Mato Grosso, 2021. n=77.

Parameter	N (%)
Health status	
Good	39 (50.65)
Very good	04 (05.19)
Regular	31 (40.26)
Poor	03 (03.90)
Comorbidities	
Yes	29 (37.66)
No	48 (62.34)
Diagnostic method	
RT-PCR	37 (48.05)
Rapid test (antigen or antibodies)	25 (32.47)
Serology	15 (19.48)
Location of testing	
Sentinel health unit	46 (59.74)
Private laboratory	21 (27.28)
Emergency Care Unit	05 (06.49)
Other	05 (06.49)
Follow-up from the basic health unit	
No	46 (59.74)
Yes	31 (40.26)
Hospitalization	
Yes	05 (06.49)
No	72 (93.51)

The most frequent clinical symptoms in the study population were: myalgia (n=44; 57.14%), fever (n=39; 50.64%), and headache (n=37; 48.05%) (Figure 1).

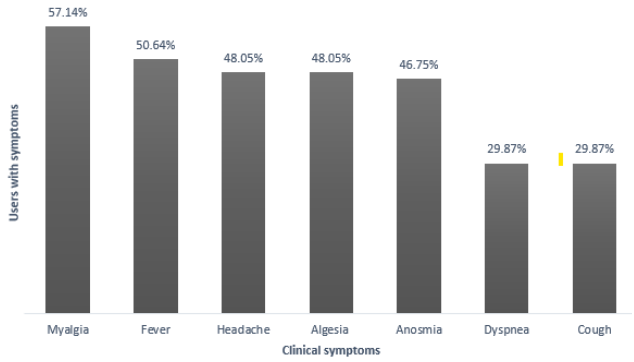

Figure 1. Clinical symptoms presented by Primary Health Care users who self-reported laboratory Covid-19 diagnosis. Rondonópolis, Mato Grosso, 2021.

DISCUSSION

This study was conducted during the second year of the Covid-19 pandemic and highlights the association between social factors and self-reported Covid-19 diagnosis among PHC users in the municipality of Rondonópolis, Mato Grosso. The study findings showed that engaging in formal and informal work was associated with a higher likelihood of self-reported Covid-19. In Brazil, eight to nine million individuals transitioned to remote work; however, over 24 million were unable to work from home, either due to informal employment or self-employment.[14] Another study emphasized that the vast majority of individuals infected by SARS-CoV-2 are workers, migrants, or people with limited access to health services or without social protection in their workplaces.[15]

Individuals engaged in formal or informal work may be more likely to contract Covid-19, as occupational exposure can increase the circulation of the virus. In Brazil, economic pressures to avoid social isolation, poor sanitary conditions in the workplace, failures in the implementation of preventive measures, and delays in vaccination have negatively impacted workers' health.[16] Adherence to biosafety measures among the working population should be intensified; moreover, it is essential to promote health education actions within PHC territories to guide this population group and prevent infections, given their higher probability of exposure to the virus.

Among the PHC users studied, those with higher monthly household income and private health insurance had a higher probability of having a laboratory diagnosis for Covid-19. These factors likely contributed to increased access to health and diagnostic services. The *Sala de Situação Fiocruz Covid nas Favelas* (FIOCRUZ Covid-19 in Favelas Situation Room) monitored epidemiological and social aspects of Covid-19 in favelas within the metropolitan area of Rio de Janeiro and found that both case numbers and deaths were higher in areas without favelas or with low favela concentration. It is believed that this pattern was related to a context of low testing coverage, in which residents of wealthier neighborhoods would be more likely to pay for diagnostic tests.[17]

The main social conditioning factors that promote inequity in access to health services are income and education. Higher income may be linked to better recognition of health needs, facilitating the search for access to health services.[18] A study using data from the Brazilian National Survey of Health identified that not having private health insurance was associated with

poor access to health services among the Brazilian population aged 19 and older.[19]

A study conducted in Wuhan, China, found that the most common symptoms in the early days of SARS-CoV-2 infection were fever, cough, dyspnea, and myalgia.6,20 These data are also confirmed in Brazilian studies.[21,22] Similarly, these clinical signs were the most prevalent among PHC users in Rondonópolis with a history of laboratory Covid-19 diagnosis. Furthermore, a significant portion of the studied population had anosmia and ageusia. In the early phases of the pandemic, these clinical manifestations were considered markers for disease screening, since they are absent in other respiratory diseases.[23]

Sentinel health units were established in Rondonópolis after the sudden increase of Covid-19 cases in the municipality, aiming to minimize transmission among the population, as well as to diagnose and treat the disease. Health units in strategic locations around the city were transformed into sentinel units to serve the population. In this research, it was observed that the sentinel network was the most sought-after health service for Covid-19 diagnosis. In this sense, the importance of the Brazilian Unified Health System (SUS) in facing the pandemic is highlighted.

The Brazilian primary health care model, structured in family health teams and with a territorial focus, was essential in the care network during the pandemic. Despite its undeniable contribution, this health system faced many challenges, such as low integration between PHC and other levels of care in the network, illness among health professionals, weak bond with users, and insufficient mediation of intersectoral actions to address social determinants.[24]

The limitations of the study include convenience sampling, which affects the homogeneity of the sample population, as well as the limited number of users who reported a Covid-19 diagnosis. Another factor to be mentioned is the self-reported diagnosis, which may suffer from recall bias, as well as the description of clinical manifestations, which were also reported without validation of clinical data. Thus, future longitudinal studies should be conducted, including a more representative sample to better contribute to the understanding of the epidemiology of Covid-19 and its impacts in the post-pandemic period.

This study demonstrates that factors associated with a positive Covid-19 diagnosis were: performing formal or informal work, higher income, and having a private health insurance plan. Mild cases of the disease predominated, and sentinel health units were the main health service used by the population in PHC territories for Covid-19 diagnosis. The results show the impact of social issues during the pandemic, in addition to highlighting the importance of services offered by SUS in this context. It is essential that public policies are formulated to ensure access to healthcare for the entire population as a way to minimize social inequalities, especially during public health crises.

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AUTHORS' CONTRIBUTIONS

Letícia Silveira Goulart contributed to the design, data analysis, writing, review, and correction of the manuscript. **Giulia Elena Tessaro** contributed to data collection and analysis, writing, and review of the manuscript. **Ingryd Rodrigues Xavier Docusse** contributed to data collection and analysis, writing, and review of the manuscript. **Ricardo Alves Olinda** contributed to the statistical analyses, review, and correction of the manuscript. **Magda de Mattos** contributed to the conception, data analysis, writing, review, and correction of the manuscript.

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

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Original Article

Factors associated with HIV infection in people with tuberculosis in Belo Horizonte, (2001-2020)

Fatores associados à infecção por HIV em pessoas com tuberculose em Belo Horizonte (2001-2020)
Factores asociados a la infección por VIH en personas con tuberculosis en Belo Horizonte (2001-2020)

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Corresponding author:
E-mail: thaissrsouza@gmail.com
Address: Professor Alfredo Balena Avenue, 190 - Santa Efigenia, Belo Horizonte, Minas Gerais, Brazil.

Thaís Rodrigues de Souza[1]
Vitória Lopes de Castro Silva[1]
Alexandra Dias Moreira[1]
Fernanda Penido Matozinhos[1]
Giselle Lima de Freitas[1]

[1]Federal University of Minas Gerais, Belo Horizonte, Minas Gerais, Brazil.

ABSTRACT

Background and Objectives: Tuberculosis (TB) remains a concern for health services. The bacillus that causes the disease can act synergistically with the Human Immunodeficiency Virus (HIV). Brazil has a high prevalence of TB and HIV, therefore, the objective of the study was to analyze the factors associated with the occurrence of TB/HIV in adults in the city of Belo Horizonte, from 2001 to 2020. **Methods:** Quantitative, cross-sectional study, whose population was composed of reported cases of TB in Belo Horizonte/MG, from 2001 to 2020. The frequencies of the variables of interest were evaluated and analysis with the chi-square test and likelihood ratio. The Poisson Regression model was developed and the prevalence ratio calculated. **Results:** A total of 23,414 cases of tuberculosis were registered and of these, 4,067 were cases of TB/HIV coinfection. Coinfection was more frequent in the homeless population (2.97%). The most prevalent associated condition was alcohol use (7.27%). The significant variables for the outcome of coinfection were male gender, age 31 to 49 years, brown race, diabetes, and drug use. **Conclusion:** The profile found confirms the relationship between coinfection and social determinants of health and reaffirms the need for intersectoral care for vulnerable groups.

Keywords: *Tuberculosis. HIV. Lung Diseases. Coinfection.*

RESUMO

Justificativa e Objetivos: A tuberculose (TB) continua sendo uma preocupação relevante para os serviços de saúde. O bacilo causador da TB pode atuar de forma sinérgica com o Vírus da Imunodeficiência Humana (HIV). O Brasil apresenta alta prevalência de TB e HIV. Assim, o objetivo do estudo foi analisar os fatores associados à ocorrência de TB/HIV em adultos no município de Belo Horizonte, de 2001 a 2020. **Métodos:** Estudo quantitativo, transversal, cuja população foi composta por casos notificados de TB em Belo Horizonte/MG, de 2001 a 2020. Foram avaliadas as frequências das variáveis de interesse e realizada análise com teste de qui-quadrado e da razão de verossimilhança. Foram desenvolvidos o modelo de Regressão de Poisson e o cálculo da razão de prevalência. **Resultados:** Foram registrados 23.414 casos de tuberculose. Destes, 4.067 são casos de coinfecção TB/HIV. A coinfecção foi mais frequente na população em situação de rua (2,97%) e o uso de álcool foi o agravo associado mais prevalente (7,27%). As variáveis significativas para o desfecho da coinfecção foram: sexo masculino, idade entre 31 e 49 anos, raça parda, diabetes mellitus e uso de drogas ilícitas. **Conclusão:** O perfil encontrado confirma a associação entre a coinfecção e os determinantes sociais da saúde, ressaltando a necessidade de atenção integrada, com foco intersetorial, às populações vulneráveis.

Descritores: *Tuberculose. HIV. Pneumopatias. Coinfecção.*

RESUMEN

Justificación y Objetivos: La tuberculosis (TB) sigue siendo una preocupación relevante para los servicios de salud. El bacilo que causa la tuberculosis puede actuar de forma sinérgica con el virus de la inmunodeficiencia humana (VIH). Brasil tiene una alta prevalencia de tuberculosis y VIH. Así, el objetivo del estudio fue analizar los factores asociados a la ocurrencia de TB/VIH en adultos en el municipio de Belo Horizonte, en el período de 2001 a 2020. **Métodos:** Se trata de un estudio cuantitativo, transversal, cuya población estuvo compuesta por casos notificados de TB en Belo Horizonte/MG, de 2001 a 2020. Se evaluaron las frecuencias de las variables de interés y se realizó el análisis con la prueba de chi-cuadrado y la razón de verosimilitud. Se desarrolló el modelo de regresión de Poisson y el cálculo de la razón de prevalencia. **Resultados:** Se registraron 23.414 casos de tuberculosis. De estos, 4.067 son casos de coinfección por tuberculosis y VIH. La coinfección fue más frecuente en la población sin hogar (2,97%) y el consumo de alcohol fue el problema asociado más prevalente (7,27%). Las variables significativas para el resultado de la coinfección fueron: sexo masculino, edad entre 31 y 49 años, raza mestiza, diabetes mellitus y consumo de drogas ilícitas. **Conclusión:** El perfil encontrado confirma la asociación entre la coinfección y los determinantes sociales de la salud, destacando la necesidad de atención integrada, con enfoque intersectorial, a las poblaciones vulnerables.

Palabras Clave: *Tuberculosis. VIH. Enfermedades pulmonares. Coinfección.*

INTRODUCTION

Tuberculosis (TB) is one of the oldest public health problems and remains a concern for health organizations and services. The World Health Organization (WHO) declared the disease a global epidemic in 1993, and reducing its burden is among the Sustainable Development Goals for 2030. However, it still causes high morbidity and mortality in many countries, including Brazil.[1,2]

TB holds significant epidemiological relevance on its own, and the causative bacillus (*Mycobacterium tuberculosis*) can act synergistically with other microorganisms, leading to coinfections, such as the association between TB and the human immunodeficiency virus (HIV). In Brazil, TB is the leading defined cause of death among people living with HIV (PLWH).[3,4]

TB/HIV coinfection creates a series of challenges for the prevention and treatment of both conditions, including therapeutic failure and immunosuppression with low CD4+ lymphocyte counts. These factors contribute to low adherence or treatment abandonment due to the high frequency of adverse or paradoxical reactions. Illness, the chain of transmission, and complications arising from both TB and HIV infections are directly related to social determinants of health, such as sex, skin color, and economic and housing conditions.[5–7]

The Brazilian Ministry of Health recommends an articulation between TB and HIV control programs to boost the detection of infections. Any individual who tests positive for one condition must be immediately tested for the other. A study has found a high number of TB notifications only post-mortem, i.e., the information was not included in official statistics. In these cases, TB and HIV were the most common causes of death. This finding indicates a weakness in the care provided and a delay in the diagnosis of patients and their contacts.[7–8]

The Brazilian Unified Health System (SUS), particularly Primary Health Care (PHC), has the reach and tools for early diagnosis, treatment, and follow-up of TB and HIV, contributing to favorable patient outcomes and reducing transmission chain. The multidisciplinary team, especially nurses, is crucial for ensuring continuity of care after diagnosis via actions such as health education. Diagnostic delays can increase mortality from coinfection and are related to both patients' late health-seeking behavior and health services failures in conducting active case finding of symptomatic individuals, especially within PHC's designated coverage areas.[10–12]

Considering that Brazil have a high prevalence of TB and HIV and recognizing the clinical and social impacts of TB/HIV coinfection — such as difficulty with therapeutic adherence, worsening clinical status, isolation, and stigma — it is essential to identify the social and clinical factors associated with its occurrence. This knowledge can aid reduce flaws in care, accelerate the interruption of the transmission chain, and promote individuals' quality of life. Thus, this study aimed to analyze the factors associated with the occurrence of TB/HIV in adults in the municipality of Belo Horizonte from 2001 to 2020.

METHODS

Study design

This was a quantitative, cross-sectional, analytical, and exploratory study.

Setting

The study setting is the municipality of Belo Horizonte, the capital of the state of Minas Gerais, with an estimated population of 2,530,701 inhabitants. In 2021, the municipality's TB/HIV coinfection rate among new TB cases was 11.7%, which was higher than that of Minas Gerais (6.9%) and the Southeast region (7.4%), but lower than the national rate (8.3%).[13,14]

Study population

The study population consisted of 23,414 TB cases reported in the Brazilian Notifiable Diseases Information System (SINAN) from 2001 to 2020. Confirmed cases of pulmonary, extrapulmonary, or both forms of TB were included, regardless of the diagnostic method used (Xpert MTB/RIF, smear microscopy, or culture), provided that the patient was a resident of the municipality under study. Extrapulmonary TB cases included pleural, lymph node, bone and joint, genitourinary, intestinal, peritoneal, pericardial, central nervous system, ocular, cutaneous, or TB affecting any other organ, whether occurring before or after primary infection. Only one record per person was included; in cases of duplicate records, the most recent was considered.

Individuals under 18 years of age and records with data inconsistencies were excluded. Inconsistency was defined as the improper completion of the field for acquired immunodeficiency syndrome (AIDS), which must be marked "yes" for HIV-positive cases. However, 60 cases were marked "no," 130 were "unknown," and 30 were blank. Those records in which a patient was simultaneously classified into two different special populations (incarcerated population and homeless population) were also excluded.

Data Collection

Data for this study were obtained from SINAN records provided by the Municipal Health Department of Belo Horizonte. The form includes patient identification, sociodemographic data (sex, age,

ethnicity/skin color, schooling level, whether the individual belongs to any special population, and whether they are a beneficiary of a social program), and the clinical profile of TB (associated conditions).

Variables

TB/HIV coinfection was the study's dependent variable, identified by a positive status for the "HIV" item.

Independent variables were categorized as sociodemographic and clinical. Sociodemographic variables included: sex (male; female), age group (18–30; 31–49; 50–60; over 60 years), ethnicity/skin color (White; Black; Yellow; Mixed-race; Indigenous), schooling level (illiterate; middle, high, and higher education—completed and incomplete), beneficiary of cash transfer programs (yes; no), and special populations (incarcerated population, homeless population, healthcare professionals, and immigrants — all with yes/no options).

Clinical variables included associated diseases and conditions: diabetes mellitus, alcohol use, mental illness, illicit drug use, and smoking habit (all with yes/no options).

Notably, information on special populations, social program beneficiaries, illicit drug use, smoking habit, and the Xpert MTB/RIF test was only included in the notification forms starting in 2015.

Data analysis

For data analysis, an Excel spreadsheet was used as a database containing only the study's variables of interest. Initially, a descriptive analysis of the sociodemographic and clinical profile of HIV-positive cases in individuals aged over 18 years was performed using absolute and relative frequencies. For variables added to the forms after 2015, frequencies were estimated based on the total of 5,654 cases reported from 2015 to 2020, of which 1,002 were HIV-positive.

Statistical analysis was performed using IBM SPSS software. The Chi-square test was applied for dichotomous variables, and the likelihood-ratio test was used for polytomous variables. Variables with a p-value <0.02 were considered statistically significant.[15] An analysis of adjusted standardized residuals was also performed to identify categories in which observed values deviated significantly from expected values (values >1.96 or <−1.96 indicate significance).[5] Finally, a multivariate Poisson regression model with robust variance was developed using variables with a p-value <0.20 in the bivariate analysis. Adjusted prevalence ratios and their respective confidence intervals were estimated. A significance level of 5% was adopted. This enabled a multivariate analysis of how these factors impact the prediction of the prevalence ratio.

Ethical aspects

The project was approved by the Research Ethics Committee of UFMG (COEP-UFMG), in accordance with Resolution No. 466/2012 of the Brazilian National Health Council and other regulatory guidelines for research involving human subjects. CAAE no. 16114619.6.0000.5149; Opinion no. 3.508.404.

RESULTS

From 2001 to 2020, 23,414 cases of tuberculosis were registered in Belo Horizonte. Of these, 4,067 tested positive for HIV, characterizing a TB/HIV coinfection. Regarding the sociodemographic profile of people with coinfection, most were male (73.7%), aged from 31 and 49 (61.9%), Mixed-race (38.5%), and had a schooling level corresponding to complete or incomplete middle school (22.8%). Only 1.8% were beneficiaries of social programs. Among the special populations, the most prevalent was the homeless population, at 2.97%. The most common associated condition was alcohol use (7.27%) (Table).

Table 1. Prevalence of tuberculosis cases with and without HIV coinfection, and p-value based on chi-square and likelihood ratio tests. Belo Horizonte, Minas Gerais, 2001 to 2020.

	HIV −	HIV +	p-value
	N (%)	N (%)	
Sex			
Female	1,068 (26.26)	6,597 (34.10)	
Male	2,999 (73.74)	1,275 (65.90)	**p<0.01‡**
Age			
18 to 30 years	845[i] (20.78)	4,755 (24.58)	
31 to 49 years	2,521[i] (61.99)	8,081[i] (41.77)	**p<0.01†**
50 to 60 years	558[i] (13.72)	3,446[a] (17.81)	
Over 60 years old	143[i] (3.52)	3,065[a] (15.84)	
Skin color			
White	976[i] (24.00)	5,289 (27.34)	
Black	646 (15.88)	2,862 (14.79)	
Yellow	17 (0.42)	117 (0.60)	
Mixed-race	1,580[a] (38.85)	6,698 (34.62)	**p<0.01†**
Indigenous	5 (0.12)	22 (0.11)	

	HIV −	HIV +	p-value
	N (%)	N (%)	
Schooling level			
Illiterate	51 (1.25)	396 (2.05)	
Incomplete and complete middle	929[a] (22.84)	5,039 (26.05)	**p<0.01†**
Incomplete and complete high school	365[a] (8.97)	2,156[i] (11.14)	
Incomplete and complete higher education	147 (3.61)	957 (4.95)	
Beneficiary*			
Yes	18 (1.80)	101 (0.52)	0.25‡
No	273 (6.71)	2,064 (10.66)	
Homeless population			
Yes	121 (2.97)	332 (1.71)	**p<0.01‡**
No	797 (19.59)	3,832 (19.80)	
Incarcerated population			
Yes	26 (0.63)	77 (0.39)	0.56‡
No	914 (22.39)	4,073 (21.05)	
Healthcare Professionals			
Yes	6 (0.14)	74 (0.38)	**0.13‡**
No	914 (0.22)	4,073 (21.05)	
Immigrants			
Yes	6 (0.14)	16 (0.08)	0.26‡
No	915 (0.22)	4,143 (21.41)	
Diabetes			
Yes	31 (0.76)	372 (1.92)	**p<0.01‡**
No	896 (22.03)	2,818 (14.56)	
Alcohol use			
Yes	296 (7.27)	1,069 (5.52)	0.24‡
No	609 (14.97)	2,225 (11.5)	
Mental disorder			
Yes	69 (1.69)	159 (0.82)	0.29‡
No	842 (20.70)	2,924 (5.11)	
Illicit drug use*			
Yes	265 (6.51)	486 (2.51)	**p<0.01‡**
No	548 (13.47)	3,274 (16.92)	
Smoking habit*			
Yes	266 (6.78)	1,211 (6.25)	**0.20‡**
No	536 (0.13)	2,707 (13.99)	

Abbreviations: ‡ Pearson's Chi-Square test for k independent samples; † Likelihood-Ratio Test; [a]Adjusted residual >1.96; [i]Adjusted residual <−1.96; HIV + = presence of HIV; HIV − = absence of HIV; *Data entered in the database after 2015.

The Poisson model with robust variance was used with the nine variables identified as having a p-value < 0.20 in the bivariate analysis. In this analysis, the variables significantly associated with the outcome of coinfection were: male sex, which showed 47.5% more cases compared to female sex (PR = 1.45; 95%CI: 1.34–1.56; p < 0.01); age group 31–49 years, which had 58.4% more cases than the group aged over 60 years (PR = 2.12; 95%CI: 1.35–2.28; p < 0.01); Mixed-race, with 14.3% more cases than White individuals (PR = 1.26; 95%CI: 0.98–1.45; p < 0.01); diabetes mellitus, with 21% more cases compared to individuals without the comorbidity (PR = 0.22; 95%CI: 0.17–0.28; p < 0.01); and illicit drug use, which showed 6.69% more cases compared to individuals who do not use such substances (PR = 3.25; 95%CI: 2.73–3.68; p < 0.01). These variables are presented in bold in the p-value column (Table 2).

Table 2. Poisson model and adjusted prevalence ratio of variables with a statistically significant difference in the study, among HIV+ cases. Belo Horizonte, Minas Gerais, 2001 to 2020.

Characteristic	Adjusted PR	95%CI	p-value
Sex			
Female	1	1	1
Male	1.45	1.34 (1.56%)	**p<0.01**
Age			
Over 60 years old	1	1	1
31 to 49 years	2.12	1.35 – 2.28	**p<0.01**
Skin color			
White	1	1	1
Mixed-race	1.26	0.98 – 1.45	**p<0.01**
Schooling level			
Incomplete and complete higher education	1	1	1
Incomplete and complete middle	1.15	1.03 – 1.67	0.25
Homeless population			
No	1	1	1
Yes	1.75	1.4 – 2.1	0.75

Characteristic	Adjusted PR	95%CI	p-value
Healthcare Professionals			
No	1	1	1
Yes	0.36	0.15 – 0.83	0.29
Diabetes			
No	1	1	1
Yes	0.22	0.17 – 0.28	**p<0.01**
Illicit drug use*			
No	1	1	1
Yes	3.25	2.73 – 3.68	**p<0.01**
Smoking habit*			
No	1	1	1
Yes	1.1	0.94 – 1.3	0.74

Abbreviations: PR: Prevalence ratio; CI: Confidence interval; *Data entered in the database after 2015.

DISCUSSION

In this study, the sociodemographic variables significantly associated with TB/HIV coinfection were male sex, younger age, being Mixed-race, low schooling level, being homeless, and being a healthcare professional. Among the associated conditions, a diagnosis of diabetes mellitus (DM), illicit drug use, and smoking habit were prominent. The prevalence of tuberculosis cases coinfected with HIV was 17.36%.

A higher number of cases occurred among males, with this group predominating in the prevalence ratio compared to females. This result may reflect men's lower engagement with health services and self-care. Studies indicate that men often associate seeking healthcare with a female practice, which contributes to vulnerabilities in male health. Research conducted in Paraíba and Rio Grande do Norte also identified a male predominance in coinfection cases. This study highlights a predisposition to early death from tuberculosis among men, which was found to occur later among women.[3,16]

The age variable was significant in this study, especially in the 31–49 years range, followed by the 18–30 years group. An integrative review of Brazilian national studies identified a predominance of coinfection in the 20–40 age group, a phase of life associated with greater exposure to risk factors such as alcohol and drug use, and unprotected sexual practices with multiple partners, which increases susceptibility to both infections.[17]

The most prevalent ethnicity/skin color in this study was Mixed-race, followed by White. The literature indicates that Black and Mixed-race people are in a situation of greater social vulnerability, with higher rates of illiteracy and lower schooling levels, based on data from the 2010 population census conducted by the Brazilian Institute of Geography and Statistics. Moreover, this group faces challenges in accessing and using healthcare services, which are often marked by discrimination and violence.[18]

The majority of coinfected individuals in this study showed a low schooling level—most being illiterate or with complete/incomplete middle school, totaling 20% of cases. This condition can compromise knowledge about the disease and, consequently, hinder the adoption of health promotion measures. Low schooling directly impacts self-care, treatment adherence, and the frequency with which an individual seeks healthcare services. Another important socioeconomic aspect to consider is the receipt of social benefits; in this study, less than 2% of patients were beneficiaries. The lack of resources for transportation or subsistence during treatment contributes to low adherence or abandonment. Social support, such as in-kind food packages and transportation vouchers, is therefore crucial. A study in Salvador showed that direct or indirect beneficiaries of social programs showed a higher TB cure rate.[7,19–20]

The special populations that showed significant differences in coinfection were the homeless population and healthcare professionals. For the homeless, three dimensions of vulnerability can be cited: individual, related to high exposure to alcohol, tobacco, and drugs; social, marked by challenges in accessing education, food, and adequate housing conditions; and policy-related, reflected in the fragility of public and institutional state resources, which can lead to treatment interruption and resistance to drug therapy. The prejudice surrounding tuberculosis and HIV is even more pronounced when the person is homeless. This population is frequently a target of social stigmas—such as associations with violence, drug use, and extreme poverty—which contributes to their avoidance of or difficulty in accessing health services.[21–22]

Regarding healthcare professionals, a study using SINAN data from Rio Grande do Sul indicated a higher prevalence of coinfection among nursing professionals. This finding may be related to the occupational risk these professionals face, which can be minimized via continuing education activities. It is essential that these workers correctly use personal protective equipment (PPE), report sharps injuries in a timely manner, and use post-exposure prophylaxis for HIV when indicated.[23]

Illicit drug use showed the highest prevalence ratio among the analyzed conditions when compared to

individuals who do not use such substances. This factor may be related to coinfection via two main mechanisms: biological, by increasing the risk of contracting infections or aggravating existing diseases; and behavioral, by compromising decision-making, encouraging risky practices, reducing treatment adherence, and negatively impacting self-care, especially regarding hygiene, nutrition, and daily routine. Individuals who abuse drugs may have an unstable routine and poor sleep quality, which directly impacts treatment effectiveness.[24]

Another condition associated with coinfection was the presence of diabetes mellitus, a condition that increases susceptibility to infections due to hyperglycemia and reduced insulin production, which compromises immune cell function. A study conducted in Minas Gerais (2006–2015) indicated a higher incidence of coinfection among individuals without diabetes; however, it also discussed complications of glycemic dysregulation, such as reduced immunity, which can be exacerbated even by the medications used to treat the disease.[5,17]

The diagnostic and treatment processes for both conditions can generate feelings of sadness, fear, stigma, and social isolation, often aggravated by the individuals' economic situation. These factors, combined with the sociodemographic profile, contribute to non-adherence or treatment abandonment. Early diagnosis, therapeutic follow-up, and retention in care require intersectoral actions capable of meeting the multiple needs of coinfected people.[25]

Populations recognized by the Brazilian Ministry of Health as special — such as incarcerated persons, the homeless, healthcare professionals, and immigrants — are at higher risk for coinfection and therefore require special attention. Each group has specific needs, lifestyles, and exposures that differ from the general population. Healthcare professionals must be prepared to manage this diversity, understanding the populations most impacted by coinfection and aligning their practices with the Ministry guidelines. It is crucial that these professionals perform timely testing for TB and HIV and promote continuity of care — essential strategies for interrupting the transmission chain of both infections.

The sociodemographic and clinical profile found in this study confirms the direct relationship between TB/HIV coinfection and social determinants of health. The findings reinforce the need for targeted care for vulnerable populations — especially Black individuals and those with low income and low schooling. Regarding the clinical profile, the importance of actions aimed at people with associated conditions is highlighted, particularly users of alcohol, illicit drugs, and tobacco.

Tools such as manuals and protocols are available to assist healthcare professionals in management and decision-making related to TB/HIV coinfection. Easily accessible diagnostic tests also contribute to early detection and the interruption of the transmission chain. It is essential to strengthen control, prevention, and treatment actions for coinfection in Primary Health Care (PHC), the ideal setting for this care. The focus should be on health promotion, monitoring of associated conditions, prevention and management of complications, treatment monitoring, and ensuring patients' quality of life.

A strength of this study was the partnership with the Municipal Health Department of Belo Horizonte and the use of the SINAN database, a robust and widely used source in Brazil for reporting health issues. A limitation was the large amount of missing data. Unfilled or "unknown" variables were excluded to avoid interfering with the associations. This challenge can be minimized by implementing continuing education programs for professionals responsible for completing notification forms, thereby ensuring greater accuracy and completeness of the information registered in the system.

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AUTHORS' CONTRIBUTIONS

Thaís Rodrigues de Souza participated in the literature search, writing of the abstract, introduction, methods, and discussion, interpretation and description of results, creation of tables and conclusions, revision, and statistical analysis. **Vitória Lopes de Castro Silva** contributed to the literature search, writing of the abstract, introduction, and discussion, interpretation and description of results, development of conclusions, revision, and statistical analysis. **Alexandra Dias Moreira** worked on the methodology, interpretation of results, development of conclusions, revision, and statistical analysis. **Fernanda Penido Matozinhos** contributed to the methodology, interpretation of results, development of conclusions, revision, and statistical analysis. **Giselle Lima de Freitas** was responsible for project administration, supervision, literature search, writing of the abstract, introduction, methods, and discussion, interpretation and description of results, development of conclusions, revision, and statistical analysis.

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

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Original Article

Mortality of elderly people with community respiratory infections associated with sepsis in an Intensive Care Unit

Mortalidade de idosos com infecção respiratória comunitária associadas à sepse em Unidade de Terapia Intensiva
Mortalidad de ancianos con infecciones respiratorias comunitarias asociadas a sepsis en una Unidad de Cuidados Intensivos

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Corresponding author:
E-mail: 20051340@uepg.br
Address: General Carlos Cavalcanti Street, 4748, Block M, Room 114, Uvaranas, Ponta Grossa, Paraná, Brazil.

Fernanda Pitome Weigert[1]
Helena Oles[1]
Caroline Palogan Reginato[1]
Erildo Vicente Muller[1]
Elis Carolina Pacheco[1]
Taís Ivastcheschen Taques[1]
Pollyana Kassia de Oliveira Borges[1]

[1]State University of Ponta Grossa, Ponta Grossa, Paraná, Brazil.

ABSTRACT

Background and Objectives: Infections in the elderly are more frequent and severe and can lead to sepsis, which can be an immediate cause of death in the Intensive Care Unit (ICU). The aim of the study was to understand the risk factors associated with the death of elderly people with sepsis admitted to the ICU due to a previous community-acquired respiratory infection. **Methods:** This is an epidemiological, descriptive and analytical study, of a mixed cohort. Medical records of elderly individuals admitted to the ICU from September 2019 to September 2020, with a diagnosis of community-acquired respiratory infection, who evolved to death due to sepsis, according to the presence or absence of Covid-19, were analyzed. Sociodemographic and clinical data were collected. Descriptive and statistical analysis was performed. **Results:** Most patients were male and between 60 and 79 years old. The presence of chronic respiratory disease (RR=1.9; p=0.014) and viral etiology (RR=3.2; p<0.001) were associated with death. **Conclusion:** The result reinforces the importance of preventing respiratory diseases in elderly people in the community, as well as early intervention to avoid worsening and death.

Keywords: *Hospital Mortality. Sepsis. Aged.*

RESUMO

Justificativa e Objetivos: As infecções em idosos são mais frequentes e graves e podem gerar sepse, que pode ser causa imediata de morte na Unidade de Terapia Intensiva (UTI). O objetivo do estudo foi compreender os fatores de risco associados ao óbito de idosos com sepse internados em UTI em decorrência de infecção respiratória comunitária prévia. **Métodos:** Este é um estudo epidemiológico, descritivo e analítico. Foram analisados prontuários de idosos, internados na UTI de setembro de 2019 a setembro de 2020, com diagnóstico de infecção respiratória comunitária, que evoluíram para óbito devido à sepse, segundo a presença ou ausência de Covid-19. Foram coletados dados sociodemográficos e clínicos. Foi realizada análise descritiva e estatística. **Resultados:** A maior parte dos pacientes era do sexo masculino e possuía entre 60 e 79 anos. A presença de doença crônica respiratória (RR=1,9; p=0,014) e a etiologia viral (RR=3,2; p<0,001) estiveram associadas à morte. **Conclusão:** O resultado reforça a importância da prevenção de doenças respiratórias em idosos na comunidade, bem como a intervenção precoce para evitar o agravamento e o óbito.

Descritores: *Mortalidade Hospitalar. Sepse. Idoso.*

RESUMEN

Justificación y Objetivos: Las infecciones en los ancianos son más frecuentes y graves y pueden derivar en sepsis, que puede ser causa inmediata de muerte en la Unidad de Cuidados Intensivos (UCI). El objetivo del estudio fue comprender los factores de riesgo asociados a la muerte de personas mayores con sepsis ingresadas en UCI por infección respiratoria comunitaria previa. **Métodos:** Se trata de un estudio epidemiológico, descriptivo y analítico, de cohorte mixta. Se analizaron las historias clínicas de personas mayores ingresadas en UCI de septiembre de 2019 a septiembre de 2020, con diagnóstico de infección respiratoria comunitaria, que fallecieron por sepsis, según presencia o ausencia de Covid-19. Se recogieron datos sociodemográficos y clínicos. Se realizó análisis descriptivo y estadístico. **Resultados:** La mayoría de los pacientes eran varones y tenían edades entre 60 y 79 años. La presencia de enfermedad respiratoria crónica (RR=1,9; p=0,014) y etiología viral (RR=3,2; p<0,001) se asociaron con la muerte. **Conclusión:** El resultado refuerza la importancia de prevenir las enfermedades respiratorias en los ancianos de la comunidad, así como la intervención temprana para prevenir su agravamiento y muerte.

Palabras Clave: *Mortalidad Hospitalaria. Sepsis. Anciano.*

INTRODUCTION

Community-acquired respiratory infections are diseases that affect the respiratory tract and are diagnosed through samples taken during the first two days of hospitalization, when not associated with a previous hospitalization at the same healthcare facility.[1,2] Among the most common infections are acute pharyngotonsillitis, rhinopharyngitis, tonsillitis, pneumonia, and Covid-19.[1] Normally, these infections can be treated on an outpatient basis, but if the symptoms worsen, the patient should be hospitalized to control the infection and prevent it from progressing to sepsis.[3]

Between 2013 and 2017, respiratory diseases accounted for almost 6 million hospitalizations in Brazil, making them the second leading cause of hospitalization in the country during that period.[4] During the same period, they accounted for 19.5% of deaths during hospitalizations.[4] In individuals over 65 years of age, this issue becomes more relevant because, among Brazilian older adults, there were more than 200,000 deaths from respiratory infections between 2012 and 2016.[4] Infections in older adults tend to be more frequent and severe, as their health is often weakened due to immune dysfunction, malnutrition, and physiological changes.[5]

Community-acquired pneumonia (CAP) is one of the leading causes of sepsis, with a short-term mortality rate of 50% in individuals receiving care in the Intensive Care Unit (ICU), and is more prevalent in the elderly.[5,6] The older adults population accounts for approximately 30 to 40% of hospitalizations for CAP.[7]

Sepsis is caused by the host's dysregulated response to infection and progresses to organ failure, consequently posing a risk to life.[8] Thus, it is one of the leading causes of morbidity and mortality worldwide and can be the immediate cause of death in ICU patients.[8]

Septic shock, in turn, is a progression of sepsis, manifesting itself through circulatory, cellular, and metabolic instability.[8] Septic shock is associated with a hospital mortality rate of > 40%.[8] To define septic shock, there must be hypotension refractory to vasopressor therapy used to increase mean arterial pressure levels to > 65 mmHg and serum lactate levels > 2 mmol/L after management of hypovolemia.[8]

Regarding sepsis in Brazil, it is estimated that there are approximately 600,000 new cases annually, with 16.5% of death certificates issued resulting from cases of this dysfunction.[9] A Brazilian study analyzed a historical series of hospitalizations for sepsis in different regions of the country and showed that the average number of hospitalizations in Brazil increased significantly between 1999 and 2016.[9] Thus, it is clear that sepsis is a challenge for the healthcare system.

Risk factors that can aggravate sepsis include longer hospital stays, comorbidities, individuals over 65 years of age, and invasive procedures.[10] When analyzing deaths in the older adults in an ICU, Alves et al. (2010) concluded that sepsis is one of the main reasons for death.[11] Between 2018 and 2022, 113,059 deaths from sepsis were recorded in Brazil. Among those who died as a result of sepsis, 37.9% were aged 80 years or older, and 21% of those hospitalized for sepsis were also in this age group.[12]

Between 2010 and 2019 in Brazil, the probability of death from sepsis among older adults was 5.6 times higher when compared to the 5-9 age group.[13] These higher rates among older adults can be explained by the presence of chronic diseases and greater functional impairment in this age group.[14]

This study can benefit the formulation of public policies, especially for hospitals, by providing an in-depth look at the older adults population, benefiting the decision-making of professionals and the learning of academics in the field of public health. However, its results reflect the reality of the older adults and the health system in a medium-sized municipality in the state of Paraná, which may be different in other locations in Brazil.

Therefore, this research was developed with the objective of understanding the risk factors associated with the death of older adults with sepsis, admitted to the ICU, resulting from a previous community-acquired respiratory infection.

METHODS

Type of study

The method chosen for the proposed analysis was an epidemiological, descriptive, quantitative, analytical and retrospective study based on medical records, carried out in an ICU at a university hospital in southern Brazil.

About the institution

The institution studied is recognized as public, offering services only to users of the Unified Health System (SUS) and provides 20 regular ICU beds and 30 ICU beds for Covid-19. In September 2019, the institution had 20 regular ICU beds. The specific beds for Covid-19 began to be implemented in March 2020, in which month there were 20 regular ICU beds and 10 Covid-19 ICU beds, with increasing progress until reaching the number mentioned in September of the same year. After the period studied, new modifications were necessary to serve society.

Participants

The study population consisted of older adults (≥ 60 years) admitted to the ICU and diagnosed with a community respiratory infection. The medical records

of patients diagnosed with a community respiratory infection who died were included in the study, cases in which the infection was acquired within the hospital were excluded, and repeated medical records and duplicate medical records were identified and excluded in order to guarantee the fidelity of the information. Those with healthcare-related infections were excluded because studies on this group already constitute a more consolidated literature, as well as involving different determinants and conditions.

Data collection

The period from September 2019 to September 2020 was determined for data collection. The period selected involved six months before and after the start of the Covid-19 pandemic, so that comparisons and scientific contributions could also be made within this theme. Data was collected using data available in the electronic medical records available in the SUS Health Care Management System.

A monthly search of ICU admissions was carried out and all medical records with primary codes in the International Statistical Classification of Diseases and Related Health Problems (ICD) related to the respiratory system were selected. ICD codes referring to the diagnosis of other sepsis were also selected. In these cases, a diagnosis of sepsis with a respiratory focus could be found, depending on the signs and symptoms. Infections related to health care were excluded from the list provided by the Hospital Epidemiology and Infection Control Center.

With the remaining medical records, those corresponding to community respiratory infection were confirmed and repeated hospitalizations recorded in the system were eliminated. Before each collection, the diagnosis of community respiratory infection was confirmed using the signs and symptoms observed in the medical records. Each patient's data was collected on the first day of admission to the ICU, and when there was no diagnosis of sepsis on the first day of admission, the patient's progress was monitored and the day of diagnosis of sepsis was also collected.

A pilot survey was carried out with three patients to check the applicability of the survey instrument. In addition, the data relating to the first twenty individuals was collected by two interviewers at the same time, in order to check that the information was consistent.

A semi-structured instrument was then drawn up with variables of interest to the study: gender, age, age group, skin color, weight, municipality of origin, chronic diseases, ICD-10, ICD-11, type of community respiratory infection, use of previous continuous use medication, etiological agent, treatment prior to infection, invasive devices, total length of hospitalization, score on the "Sequential Organ Failure Assessment" (SOFA), score on the "Quick Sequential Organ Failure Assessment" (qSOFA); sepsis using "Sepsis-3" consensus criteria; sepsis using "Systemic Inflammatory Response Syndrome" (SIRS) criteria according to the Latin American Sepsis Institute (ILAS); diagnosis of sepsis in medical records; septic shock.

All individuals who reported, or whose medical records described, consultation with a health professional or use of prescription medication prior to being hospitalized were considered to be users of previous treatment for infection prior to hospitalization. As early treatment for Covid-19 is not consolidated in the international literature as valid, it was decided not to verify this information among Covid-19 patients.

In this study, we described the conditions investigated among older adults whose cases of community respiratory infection progressed and died of sepsis, according to the presence or absence of Covid-19, which includes other community respiratory infections such as influenza, pneumonia, bronchitis, among others. We chose to describe the patients according to their Covid-19 status because this infection has the characteristics of viral sepsis, sometimes with the distinction of bacterial sepsis.

In this study, the diagnosis of community respiratory infection was based on the ICD-10 criteria recorded in the medical records.

Covid-19 was diagnosed according to a positive Reverse Transcription Polymerase Chain Reaction (RT-PCR) test or a characteristic chest CT scan described in the medical records.

The definition of sepsis followed the ILAS consensus, as the presence of a known disease or suspected infection and acute organ dysfunction, and also the definitions of the third international sepsis consensus (Sepsis-3), as suspected or certain infection and an acute increase ≥ 2 points in SOFA in response to an infection, representing organ dysfunction.[15, 16]

SOFA is a score that assesses respiratory, hematological, hepatic, cardiovascular and neurological functions with daily observation, its score ranges from zero to four for each item assessed, and a maximum final sum of 24 points can be obtained, with the highest score indicating greater severity of the septic condition.[16]

The qSOFA score has the following criteria: systolic blood pressure lower than 100 mmHg, respiratory rate higher than 22/min and altered mental state, such as a Glasgow Coma Scale score <15.[17] Each variable counts for one point, so the score ranges from 0 to 3, and the higher the score, the higher the risk of mortality.[18]

Data analysis

The quantitative data was organized in a Microsoft Excel® spreadsheet and then analyzed using the IBM-SPSS® statistical package, version 22. Categorical

variables were expressed as frequencies and percentages, and continuous variables were expressed as medians and interquartile ranges. The Shapiro-Wilk and Kolmogorov-Smirnov tests were used to test the normality of the variables. The association between the exposure and outcome variables was assessed using the chi-square test and the relative risk association measure for categorical variables. For numerical variables, Student's t-test and the Mann-Whitney U-test were used. Results were considered statistically significant when $p<0.05$.

Ethical aspects

This study is part of the research entitled "Studies on health surveillance, mortality and hospital epidemiology". The research project was evaluated and approved by the Hospital's Institutional Research Committee and analyzed and approved by the Human Research Ethics Committee of the State University of Ponta Grossa, Uvaranas Campus (CAAE: 99995518.4.0000.0105), by opinion no. 4.110.879 on March 29, 2022.

RESULTS

The medical records selection process is described in figure 1. A total of 1,473 hospitalizations were found between September 2019 and September 2020 related to respiratory system diseases and sepsis. Of these, 893 (60.6%) were related to hospitalizations of the older adults, of which 229 (15.5%) were associated with a diagnosis of community respiratory infection. Of this sample, 125 patients died (8.5%) (Figure 1).

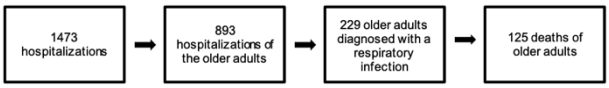

Figure 1. Process of selecting medical records, until reaching the sample studied, at a University Hospital in a municipality in southern Brazil, 2021.

In the period analyzed, 125 (54.58%) older adults hospitalized due to community respiratory infection died. 89 (71.2%) older adults had Covid-19 and 36 (28.8%) had other infections, of which 34 (94.4%) were classified as pneumonia, one (2.8%) as flu and one (2.8%) as bronchitis.

With regard to Covid-19, the sample was predominantly made up of men (56.2%), aged between 60 and 79 (79.8%), white (84.3%) and living in the municipality of Ponta Grossa (PR) (70.8%). Regarding clinical aspects, it was observed that the majority had some chronic disease (86.5%), with emphasis on chronic cardiovascular disease (71.9%), diabetes mellitus (34.8%) and chronic respiratory disease (22.5%). In addition, 75 (84.3%) of the older adults with Covid-19 had previously used some form of continuous medication (Table 1).

Of the patients with other community respiratory infections (except Covid-19), the data shows that the majority were male (52.8%), aged between 60 and 79 (66.7%), white-skinned (88.9%) and living in Ponta Grossa (PR) (55.6%). It was observed that 31 (86.1%) individuals had pre-existing chronic morbidity, including cardiovascular disease (66.7%), respiratory disease (44.4%), diabetes mellitus (27.8%) and neurological disease (16.7%). It was also found that 28 (77.8%) were on continuous medication (Table 1).

Table 1. Sociodemographic and clinical characteristics of older adults who died with a diagnosis of community respiratory infection, according to the presence or absence of Covid-19 (n=125), in an Intensive Care Unit of a University Hospital in a municipality in southern Brazil, 2021.

Variable		Presence of Covid-19 N/total (%)	Absence of Covid-19 N/total (%)
Gender	Male	50 (56.2)	19 (52.8)
	Female	39 (43.8)	17 (47.2)
Age group	≥ 80 years	18 (20.2)	12 (33.3)
	60 to 79 years	71 (79.8)	24 (66.7)
Skin color	Other	14 (15.7)	4 (11.1)
	White	75 (84.3)	32 (88.9)
Municipality of origin	Ponta Grossa	63 (70.8)	20 (55.6)
	Other	26 (29.2)	16 (44.4)
Comorbidities	Yes	77 (86.5)	31 (86.1)
	No	12 (13.5)	5 (13.9)
Dyslipidemia	Yes	6 (6.7)	0 (0)
	No	83 (93.3)	36 (100)
Chronic kidney disease	Yes	2 (2.2)	1 (2.8)
	No	87 (97.8)	35 (97.2)
Chronic endocrine disease	Yes	9 (10.1)	2 (5.6)
	No	80 (89.9)	34 (94.4)

Variable		Presence of Covid-19 N/total (%)	Absence of Covid-19 N/total (%)
Chronic neurological disease	Yes	18 (20.2)	6 (16.7)
	No	71 (79.8)	30 (83.3)
Chronic immunological disease	Yes	1 (1.1)	0 (0)
	No	88 (98.9)	36 (100)
Obesity	Yes	1 (1.1)	1 (2.8)
	No	88 (98.9)	35 (97.2)
Chronic respiratory disease	Yes	20 (22.5)	16 (44.4)
	No	69 (77.5)	20 (55.6)
Neoplasm	Yes	3 (3.4)	1 (2.8)
	No	86 (96.6)	35 (97.2)
Diabetes mellitus	Yes	31 (34.8)	10 (27.8)
	No	58 (65.2)	26 (72.2)
Chronic cardiovascular disease	Yes	64 (71.9)	24 (66.7)
	No	25 (28.1)	12 (33.3)
Etiological agent*	Virus	83 (93.3)	1 (6.7)
	Bacteria, fungi, both	6 (6.7)	14 (93.3)
Previous continuous use medication	Yes	75 (84.3)	28 (77.8)
	No	14 (15.7)	8 (22.2)

Abbreviations: *Information unavailable for 21 individuals (16.8%) of the study population.

We found that 76 (85.4%) older adults with Covid-19 were admitted to the ICU with ICD-10 diagnoses from Chapter I (which includes infectious and parasitic diseases), and of these, 54 (71.2%) had the primary ICD code B34.2 (coronavirus infection of unspecified location). In addition, 5 (5.6%) of them had diagnoses from Chapter X (related to diseases of the respiratory system) (Table 2).

It was noted that 88 (98.9%) individuals with Covid-19 were using a circulatory invasive device, 86 (96.6%) respiratory, 60 (67.4%) nutritional and 60 (67.4%) were using a bladder catheter. Almost all (75.3%) used up to three invasive devices simultaneously (Table 2).

As for the diagnosis of sepsis, 47 (52.8%) did not have a medical diagnosis in their medical records, but when Covid-19 patients were assessed according to the ILAS and SOFA diagnostic criteria, 89 (100%) and 87 (97.8%), respectively, met the requirements for sepsis (Table 2).

Among the older adults with other respiratory infections, 28 (77.8%) were diagnosed with ICD-10 Chapter X pathologies on admission, while 4 (11.1%) had ICD-10 Chapter 1 pathologies. Regarding the use of invasive devices, 35 (97.2%) of the patients used a circulatory invasive device, 35 (97.2%) used a respiratory invasive device, 24 (66.7%) used an enteral tube and 23 (63.9%) used a bladder tube. In addition, 30 (83.3%) of the patients who did not have Covid-19 used up to three invasive devices concomitantly (Table 2).

When the SOFA and ILAS scores were assessed, 35 (97.2%) of the older adults who did not have Covid-19 met the requirements for sepsis according to the Sepsis-3 consensus and 36 (100%) met the ILAS requirements (Table 2).

Table 2. Characteristics related to the care of older adults who died with a diagnosis of community respiratory infection according to the presence or absence of Covid-19 (n=125) in the Intensive Care Unit of a University Hospital in a municipality in southern Brazil, 2021.

Condition		Presence of Covid-19 N/total (%)	Absence of Covid-19 N/total (%)
Admission diagnosis (ICD-10)	XXI*	0 (0)	1 (2.8)
	X **	5 (5.6)	28 (77.8)
	I ***	76 (85.4)	4 (11.1)
	XXII****	4 (4.5)	3 (8.3)
	XVIII*****	4 (4.5)	0 (0)
Admission diagnosis (ICD-11)	24******	0 (0)	1 (2.8)
	12*******	5 (5.6)	28 (77.8)
	1********	76 (85.4)	4 (11.1)
	25*********	4 (4.5)	3 (8.3)
	21**********	4 (4.5)	0 (0)

Condition		Presence of Covid-19 N/total (%)	Absence of Covid-19 N/total (%)
Sepsis according to Sepsis-3 consensus criteria	Yes	87 (97.8)	35 (97.2)
	No	2 (2.2)	1 (2.8)
Sepsis by ILAS criteria	Yes	89 (100)	36 (100)
Diagnosis of sepsis in medical records	No	47 (52.8)	21 (58.3)
	Yes	42 (47.2)	15 (41.7)

Abbreviations: *XXI - Factors influencing health status and contact with health services; **X - Diseases of the respiratory system; ***I - Certain infectious and parasitic diseases; ****XXII - Special purpose codes; *****XVIII - Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified; ******24 - Factors influencing health status or contact with health services; *******12 - Diseases of the respiratory system; ********1 - Certain infectious or parasitic diseases; *********25 - Special purpose codes; **********21 - Symptoms, signs or clinical findings, not elsewhere classified.

Older adults admitted to the ICU with a diagnosis of community respiratory infection and infected with Covid-19 had a median age of 73 years (IQR=11; p=0.175), and weighed 74 kg (IQR=30; p=0.147). The median number of days spent in the ICU was eight days (IQR=5; p=0.937). The median SOFA and qSOFA scores were eight (IQR=5; p=0.568) and one (IQR=1; p=0.366) on the first day of hospitalization respectively (Table 3).

The older adults admitted to the ICU for other respiratory infections, except Covid-19, had a median age of 75 years (IQR=14) and weighed 65.0 kg (IQR=38). The median number of days spent in the ICU was 12 days (IQR=13), and the calculated SOFA and qSOFA scores were expressed as a median of eight points (IQR=6) and one point (IQR=1), respectively (Table 3).

Table 3. Table with the bivariate analysis of the continuous variables analyzed of older adults who died with a diagnosis of community respiratory infection, according to the presence or absence of Covid-19 (n=125) in the Intensive Care Unit of a University Hospital in a municipality in southern Brazil, 2021.

Variable	Presence of Covid-19 MD* (IQR*)	Absence of Covid-19 MD (IQR)	Total MD (IQR)	*p-value*
Age (years)	73.0 (11.0)	75.0 (14.0)	75.0 (11.0)	0.175
Weight (kg)	74.0 (30.0)	65.0 (38.0)	69.5 (32.5)	0.147
Total length of stay in ICU (days)	8.0 (5.0)	12.0 (13.0)	8.0 (8.0)	0.937
SOFA score (points)	8.0 (5.0)	8.0 (6.0)	8.0 (6.0)	0.568
qSOFA score (point)	1.0 (1.0)	1.0 (1.0)	1.0 (1.0)	0.366

Abbreviations: *MD – median; **IQR - interquartile range.

The most frequent characteristics related to mortality and Covid-19 were the presence of chronic respiratory disease (55.6%) and the type of etiologic agent (98.8%). The risk of death from Covid-19 in older adults who had a previous chronic respiratory disease and were diagnosed with sepsis at the start of hospitalization was 1.9 times higher compared to individuals without comorbidity (p=0.014). Infection by a viral etiological agent proved to be 3.2 times more fatal than other pathological agents in the presence of Covid-19 (p<0.001) (Table 4).

Table 4. Bivariate analysis of the sociodemographic and clinical characteristics of older adults who died with a diagnosis of community respiratory infection (n=125) in an Intensive Care Unit at a University Hospital in a municipality in southern Brazil, 2021.

Variable		Presence of Covid-19 N/total (%)	Absence of Covid-19 N/total (%)	RR* (**95% CI)	*p-value*
Gender	Male	50/69 (72.5)	19/69 (27.5)	1.0 (0.8-1.3)	0.729
	Female	39/56 (69.6)	17/56 (30.4)	Ref.	
Age group	≥ 80 years	18/30 (60)	12/30 (40)	0.8 (0.5-1.1)	0.12
	60 to 79 years	71/95 (74.7)	24/95 (25.3)	Ref.	
Skin color	Other	14/18 (77.8)	4/18 (22.2)	1.1 (0.8-1.4)	0.586
	White	75/107 (70.1)	32/107 (29.9)	Ref.	
Municipality of origin	Ponta Grossa	63/83 (75.9)	20/83 (24.1)	1.2 (0.9-1.6)	0.103
	Other	26/42 (61.9)	16/42 (38.1)	Ref.	
Chronic diseases	Yes	77/108 (71.3)	31/108 (28.7)	1.0 (0.7-1.4)	0.952
	No	12/17 (70.6)	5/17 (29.4)	Ref.	
Dyslipidemia	Yes	6/6 (100)	0/6 (0)	1.4 (1.2-1.6)	0.181
	No	83/119 (69.7)	36/119 (30.3)	Ref.	
Chronic kidney disease	Yes	2/3 (66.7)	1/3 (33.3)	0.9 (0.4-2.0)	1
	No	87/122 (71.3)	35/122 (28.7)	Ref.	
Chronic endocrine disease	Yes	9/11 (81.8)	2/11 (18.2)	1.1 (0.8-1.5)	0.509
	No	80/114 (70.2)	34/114 (29.8)	Ref.	

Variable		Presence of Covid-19 N/total (%)	Absence of Covid-19 N/total (%)	RR* (**95% CI)	*p-value*
Chronic neurological disease	Yes	18/24 (75)	6/24 (25)	1.0 (0.8-1.3)	0.647
	No	71/101 (70.3)	30/101 (29.7)	Ref.	
Chronic immunological disease	Yes	1/1 (100)	0/1 (0)	1.4 (1.2-1.5)	1
	No	88/124 (71)	36/124 (29)	Ref.	
Obesity	Yes	1/2 (50)	1/2 (50)	0.6 (0.1-2.8)	0.504
	No	88/123 (71.5)	35/123 (28.5)	Ref.	
Chronic respiratory disease	Yes	20/36 (55.6)	16/36 (44.4)	1.9 (1.1-3.3)	0.014
	No	69/89 (77.5)	20/89 (22.5)	Ref.	
Neoplasm	Yes	3/4 (75)	1/4 (25)	1.0 (0.5-1.8)	1
	No	86/121 (71.1)	35/121 (28.9)	Ref.	
Diabetes mellitus	Yes	31/41 (75.6)	10/41 (24.4)	1.0 (0.8-1.3)	0.447
	No	58/84 (69)	26/84 (31)	Ref.	
Chronic cardiovascular disease	Yes	64/88 (72.7)	24/88 (27.3)	1.0 (0.8-1.3)	0.561
	No	25/37 (67.6)	12/37 (32.4)	Ref.	
Etiologic agent	Virus	83/84 (98.8)	1/84 (1.2)	3.2 (1.6-6.4)	<0.001
	Bacteria, fungi, both	6/20 (30)	14/20 (70)	Ref.	
Previous continuous use medication	Yes	75/103 (72.8)	28/103 (27.2)	1.1 (0.8-1.6)	0.388
	No	14/22 (63.6)	8/22 (36.4)	Ref.	
Number of invasive devices	4 or more	22/28 (78.6)	6/28 (21.4)	1.1 (0.8-1.4)	0.328
	Up to 3	67/97 (69.1)	30/97 (30.9)	Ref.	
Sepsis according to Sepsis-3 consensus criteria	Yes	87/122 (71.3)	35/122 (28.7)	1.0 (0.4-2.4)	1
	No	2/3 (66.7)	1/3 (33.3)	Ref.	
Diagnosis of sepsis in medical records	No	47/68 (69.1)	21/68 (30.9)	0.9 (0.7-1.1)	0.574
	Yes	42/57 (73.7)	15/57 (26.3)	Ref.	

Abbreviations: *RR - risk ratio; **CI - confidence interval.

DISCUSSION

In this study, 69 men (55.2%) died, compared to 56 women (44.8%). Men tend to spend more time in the ICU and receive more interventions during hospitalization, such as the initiation of antibiotics.19 One explanation for the higher number of deaths in men could be behavioral, since men adhere less to preventive health care and visit health services less regularly.[19] Therefore, when they enter hospitals, they tend to have more serious cases that require ICU admission.

With regard to age group, there was a higher rate of community respiratory infection associated with sepsis and death in older adults aged between 60 and 79. This result is corroborated by a study carried out in a large hospital in the municipality of Fortaleza, Ceará, which showed that there was a higher number of deaths in patients aged around 60 with respiratory sepsis.[20] A possible explanation could be the higher prevalence of older adults Brazilians aged between 60 and 79, compared to those aged 80 or over. According to the Brazilian Institute of Geography and Statistics (IBGE), in 2021, 14.2% of the Brazilian population was made up of individuals aged 60-79, while 2.1% of individuals were aged 80 or over.[21]

In a study conducted in China, it was shown that, in 2018, 18% of patients with pneumonia who were discharged from hospital were over 60 years old.[5] However, when analyzing the profile of individuals hospitalized for infectious diseases between 2013 and 2017 in this same study, it was found that the older adults aged 85 to 89 had a much higher risk of respiratory diseases than those aged 60 to 64.[5]

Regarding clinical aspects, most patients had some associated chronic disease, the most common being cardiovascular, diabetes mellitus and chronic respiratory diseases. In the pandemic caused by Covid-19, patients with cardiovascular disease were found to be more susceptible to the virus, as well as having a higher mortality rate.[22] Diabetes mellitus, systemic arterial hypertension and neoplasms are prevalent pathologies in patients with sepsis.[23] These diseases can cause physiological changes that culminate in endothelial dysfunction, thus affecting the condition of individuals with community respiratory infection associated with sepsis.[23] Hyperglycemia resulting from diabetes mellitus can induce oxidative stress, with a consequent increase in free radicals and endothelial dysfunction.[23] Neoplasms, in turn, can lead to an increase in nitric oxide production in the body, as well as other changes, resulting in a pro-inflammatory state with a propensity for endothelial dysfunction.[23] Systemic arterial hypertension can also lead to heart failure, which can be harmful to patients with community infection and sepsis.[23]

Airway diseases are responsible for high morbidity and mortality rates, especially at the extremes of age.[4] A

study carried out in six academic hospitals in the United States, from January 2017 to March 2018, showed that deaths from sepsis in ICUs were 37.5%.[24] Patients had an average age of 60.5 years and those with pre-existing chronic diseases were 40.3%, a rate that is similar to that of this study.[24] The comorbidities that may have contributed to death were chronic heart disease (15.3%) and chronic lung disease (9.0%), among other diseases.[24]

Covid-19 infection was the most common among the other etiological agents. Covid-19 is a viral pulmonary infection that emerged in 2019 and has had a major impact worldwide.[25] It has high transmissibility and lethality, observed mainly in with underlying comorbidities and advanced age.[25] In the state of Paraná, the older adults were very affected by the infection, with a lethality rate of around 17.81% in 2020.[25]

The epidemiological bulletin published by the Paraná State Health Department (SESA) reported that, as of September 30, 2020, a period concurrent with the one studied in this research, there were 6,417 confirmed cases and 139 deaths of patients with Covid-19 in the municipalities that make up the 3rd Health Region of Paraná - the territory served by the hospital unit investigated.[26]

In addition to Covid-19, it was also highlighted that a high number of individuals entered the ICU with CAP. The study can be compared to the result found in a study carried out in Portugal between 2000 and 2014, which evaluated the hospital mortality rate due to CAP.[27] The study showed that mortality was 18.5% over the entire period, with 56.2% of individuals being male and 91.7% aged over 65.27 However, in this study, mortality due to CAP was almost double the rate found in Portugal.[27]

Infection by a viral etiologic agent was associated as a risk factor for death in the older adults with sepsis, which may be justified by the population and the period studied, coinciding with part of the Covid-19 pandemic. In a study carried out in a network of hospitals in 30 provinces in China between 2009 and 2020, it was found that both children and the older adults had a higher rate of bacterial and viral co-infections in patients with severe community-acquired pneumonia when compared to patients without this diagnosis.[28]

The use of previous continuous medication was shown to have a high incidence among patients with community respiratory infection who died. Older adults over the age of 80 have a high percentage of ICU admissions.[29] The presence of multiple comorbidities and polypharmacy, which are common in this age group, are associated with higher long- and short-term mortality.[29] It is therefore important to encourage the rational use of medication and to encourage vaccination, in order to prevent a respiratory disease that could easily be treated in primary care from worsening and causing hospitalization.

The most frequent primary diagnoses were those contained in Chapter I - "Some infectious and parasitic diseases", and Chapter X - "Diseases of the respiratory system", of the ICD-10. This result was obtained due to the inclusion criterion in this study based on community respiratory infection and because the study was carried out during the Covid-19 pandemic period. According to the SUS Hospital Information System (SIH/SUS), the mortality rate for older adults aged 60-79 in the state of Paraná in September 2020, a period consistent with that studied in this research, for diseases contained in Chapter I of ICD-10 was 17.97%, while mortality from causes contained in Chapter X was 13.08%.30

The majority of older adults with sepsis and community respiratory infection met criteria according to the Sepsis-3 and ILAS consensus. A 2022 study of patients with sepsis found that the primary outcome in this population was clinical deterioration 72 hours after admission, as well as secondary outcomes such as death and ICU admission, with the SOFA score increasing by at least 2 points.[31] In this same study, it was found that patients who had clinical worsening stayed longer in the ICU.[31] The median number of days that older adults patients with community respiratory infection and sepsis spent in the ICU was 8 days in this study. It should be noted that the longer a patient stays in the ICU, the greater their exposure to the hospital environment, which increases the chances of infections and, consequently, the development of sepsis and death.

Community respiratory infections were classified according to the primary ICD described by the physician in the medical record as the diagnosis of hospitalization, given that respiratory infections have clinical pictures that are easy to characterize. Thus, it was considered less harmful to the quality of the information to include cases with respiratory symptoms than to exclude cases that could have been admitted for another cause diagnosed by the doctor at the time of admission.

It is suggested that future research should compare this study with others containing patients with similar characteristics who survived sepsis, so that more robust comparisons can be made on the subject.

The findings of this study reflect the impacts that the Covid-19 pandemic has had on hospital institutions, both ICUs and healthcare teams. Community respiratory infections, more specifically Covid-19, are a challenge for public health due to their complexity. Because of this, the research provides new insights into the conditions that result in sepsis in older adults with Covid-19, which could guide the implementation of new studies on the subject, as well as helping in the management of patients with Covid-19 and sepsis.

Educational practices in primary health care could encourage self-care among the older adults, mutual support between professionals and the population, and improve adherence to appointments, vaccinations and the use of medication to prevent the older adults with chronic respiratory diseases from developing infections and requiring future hospital intervention. In a study published in 2025, it was found that among the 5,296 older adults with cardiovascular diseases who took part in the research, 76.6% had been vaccinated against influenza. A high percentage of unvaccinated older adults can have an impact on the burden of morbidity and mortality. Influenza, for example, can be an aggravating factor in underlying comorbidities because it raises levels of pro-inflammatory cytokines, aggravates symptoms and contributes to an increase in overall mortality.[32]

This study has limitations regarding the lack of data on the patients studied, such as mean arterial pressure and vital signs, which were not included in electronic medical records and which were not collected in physical medical records due to the pandemic. However, it is justified that the presence of such data would not eliminate the sepsis conditions detected and would not improve the clinical picture; on the contrary, if present, they could worsen the SOFA and ILAS scores. In addition, this study was carried out in a single center, therefore, it is not possible to generalize the results found.

The results of this study indicate the need to implement and improve public policies related to immunization and general health of the older adults. The epidemiological information revealed in this research confirms the diagnosis of worse progression of septic conditions among the older adults, when admitted to the ICU. Therefore, the study is relevant for the clinical management of sepsis in a hospital environment and also for reflection on means of preventing hospitalizations due to community-acquired respiratory infections among the older adults, since the study revealed that the incidence of mortality in older adults admitted to the ICU due to community-acquired respiratory infection with sepsis was high. The factors that were associated with mortality were: the viral etiological agent and the presence of pre-existing chronic respiratory disease. Therefore, the need for public policies that corroborate the expansion of vaccination coverage among the older adults is reinforced, given the ability to prevent severe respiratory infections.

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AUTHORS' CONTRIBUTIONS

Fernanda Pitome Weigert contributed to the conception and design or analysis and interpretation of data, writing of the article or relevant critical review of intellectual content, final approval of the version to be published, was responsible for all aspects of the work in ensuring the accuracy and integrity of any part of the work. **Helena Oles** contributed to the conception and design or analysis and interpretation of data, writing of the article or relevant critical review of intellectual content, final approval of the version to be published, was responsible for all aspects of the work in ensuring the accuracy and integrity of any part of the work. **Caroline Palogan Reginato** contributed to the conception and design or analysis and interpretation of data, writing of the article or relevant critical review of intellectual content, final approval of the version to be published, was responsible for all aspects of the work in ensuring the accuracy and integrity of any part of the work. **Erildo Vicente Müller** contributed to the conception and design or analysis and interpretation of data, writing of the article or relevant critical review of intellectual content, final approval of the version to be published, was responsible for all aspects of the work in ensuring the accuracy and integrity of any part of the work. **Taís Ivastcheschen Taques** contributed to the conception and design or analysis and interpretation of data, writing of the article or relevant critical review of the intellectual content, final approval of the version to be published, was responsible for all aspects of the work in ensuring the accuracy and

integrity of any part of the work. **Pollyana Kassia de Oliveira Borges** contributed to the conception and design or analysis and interpretation of data, writing of the article or relevant critical review of the intellectual content, final approval of the version to be published, was responsible for all aspects of the work in ensuring the accuracy and integrity of any part of the work.

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

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Original Article

Temporal trend of tuberculosis in children under 15 years of age in the state of Paraná

Tendência temporal da tuberculose em menores de 15 anos no estado do Paraná
Tendencia temporal de la tuberculosis en menores de 15 años en el estado de Paraná

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Corresponding author:
E-mail: alessandro.scholze@ufsm.br
Address: Building 19 - Roraima Avenue, 1000, Camobi, Santa Maria, Rio Grande do Sul, Brazil.

Alessandro Rolim Scholze[1]
Camila da Cruz Rodrigues[2]
Kelly Holanda Prezotto[3]
Carolina Fordellone Rosa Cruz[2]
Josilene Dália Alves[4]
Leonardo Bigolin Jantsch[5]
Rosana Rosseto de Oliveira[2]
Flavia Meneguetti Pieri[6]
Emiliana Cristina Melo[2]

[1]Federal University of Santa Maria, Santa Maria, Rio Grande do Sul, Brazil.
[2]State University of Northern Paraná, Bandeirantes, Paraná, Brazil.
[3]State University of Central-West Paraná, Guarapuava, Paraná, Brazil.
[4]Federal University of Mato Grosso, Barra do Garças, Mato Grosso, Brazil.
[5]Federal University of Santa Maria, Palmeira das Missões, Rio Grande do Sul, Brazil.
[6]State University of Londrina, Londrina, Paraná, Brazil.

ABSTRACT

Background and Objectives: Childhood tuberculosis is a neglected disease at a global level, and it remains invisible in the scientific literature. This study aims to analyze the temporal trend of tuberculosis in individuals under 15 years of age in the state of Paraná, Brazil. **Methods:** An ecological time series study conducted across the 399 municipalities of Paraná state. The population consisted of all reported cases of childhood tuberculosis (children under 15 years of age) registered in the Notifiable Diseases Information System from January 1, 2013, to December 31, 2022. The variables analyzed included age, sex, race/ethnicity, area of residence, type of case entry, clinical form, laboratory confirmation, sputum bacilloscopy, and case outcome. Descriptive statistical analysis was performed, including absolute and relative frequency calculations, along with time series analysis using the Prais-Winsten generalized linear regression method. **Results:** A total of 592 cases of childhood tuberculosis were reported. Among these, 194 (32.8%) were aged 10 to 14 years, 144 (24.3%) were under one year of age, 142 (24.0%) were aged one to four years, and 112 (18.9%) were aged five to nine years. The Prais-Winsten analysis indicated that the temporal trend remained stationary for all variables analyzed. **Conclusion:** The trend of childhood tuberculosis in Paraná is stationary, highlighting the need to strengthen TB control strategies within health services to improve case detection, diagnosis, and treatment.

Keywords: *Child Health. Adolescent Health. Tuberculosis. Public Health. Time-Series Studies.*

RESUMO

Justificativa e Objetivos: A tuberculose infantil é uma doença negligenciada em nível mundial que apresenta invisibilidade em relação a trabalhos científicos na área. Este estudo visa analisar a tendência temporal da tuberculose em menores de 15 anos no estado do Paraná. **Métodos:** Estudo ecológico de séries temporais, desenvolvido nos 399 municípios do Paraná. A população foi composta por todos os casos notificados de tuberculose infantil (idade menor que 15 anos) no Sistema de Informação de Agravos de Notificação, no período de 01 de janeiro de 2013 a 31 de dezembro de 2022. As variáveis incluídas foram a idade, sexo, raça/cor, zona de residência, tipo de entrada, forma clínica, confirmação laboratorial, baciloscopia de escarro e situação de encerramento. Utilizou-se a análise estatística descritiva e cálculo da frequência absoluta e relativa com aplicação de séries temporais e método de regressão linear generalizada de *Prais-Winsten*. **Resultados:** Foram notificados 592 casos de tuberculose infantil, destes, 194 (32,8%) casos tinham de dez a 14 anos, 144 (24,3%) tinham idade inferior a um ano, 142 (24,0%) de um a quatro anos e 112 (18,9%) de cinco a nove anos. Ao analisar a regressão de *Prais-Winsten*, identificou-se que a tendência temporal se apresentou estacionária para todas as variáveis de análise. **Conclusão:** A tendência da tuberculose infantil encontra-se estacionária no Paraná, evidenciando a importância da ampliação das estratégias de combate a TB nos serviços de saúde para detecção, diagnóstico e tratamento.

Descritores: *Saúde da criança. Saúde do Adolescente. Tuberculose. Saúde pública. Estudos de séries temporais.*

RESUMEN

Justificación y Objetivos: La tuberculosis infantil es una enfermedad desatendida a nivel mundial, que presenta invisibilidad en cuanto a la producción científica en el área. Este estudio tiene como objetivo analizar la tendencia temporal de la tuberculosis en menores de 15 años en el estado de Paraná, Brasil. **Métodos:** Estudio ecológico de series temporales, desarrollado en los 399 municipios del estado de Paraná. La población estuvo compuesta por todos los casos notificados de tuberculosis infantil (niños menores de 15 años) en el Sistema de Información de Agravamientos de Notificación, en el período del 1 de enero de 2013 al 31 de diciembre de 2022. Las variables incluidas fueron: edad, sexo, raza/color, zona de residencia, tipo de entrada, forma clínica, confirmación por laboratorio, baciloscopia de esputo y situación de cierre del caso. Se utilizó análisis estadístico descriptivo, con cálculo de frecuencias absolutas y relativas, y análisis de series temporales mediante el método de regresión lineal generalizada de Prais-Winsten. **Resultados:** Se notificaron 592 casos de tuberculosis infantil; de estos, 194 (32,8%) correspondían al grupo de 10 a 14 años, 144 (24,3%) eran menores de un año, 142 (24,0%) tenían entre uno y cuatro años, y 112 (18,9%) entre cinco y nueve años. Según el análisis de Prais-Winsten, se identificó que la tendencia temporal fue estacionaria para todas las variables analizadas. **Conclusión:** La tendencia de la tuberculosis infantil en el estado de Paraná se mantiene estacionaria, lo que resalta la importancia de ampliar las estrategias de combate a la tuberculosis infantil en los servicios de salud, con miras a mejorar la detección, diagnóstico y tratamiento oportuno de los casos.

Palabras Clave: *Salud Infantil. Salud del Adolescente. Tuberculosis. Salud pública. Estudios de Series Temporales.*

INTRODUCTION

Tuberculosis (TB) is an ancient disease and represents a serious public health problem at present, affecting different populations, including children.[1] In 2022, childhood tuberculosis reached 1.3 million children under 15 years of age, accounting for about 12% of all cases worldwide.[2] In 2023, 80,012 new cases of TB were notified in Brazil, from which 3.6% (3,409 cases) occurred in children under 15 years old. From those, 36.6% (1,248) were under five years old, 23.1% (789) from five to 10 years of age, and 40.2% (1,372) from 11 to 15 years old. In the state of Paraná, during the same period, 2,246 new cases of TB were notified, from which 77 (3.4%) occurred in children under the age of 15.[3]

Childhood TB in Brazil is a neglected disease. Despite of the treatment success being high (88%), it is observed a low detection rate in this age group, with an estimated 65% of cases undiagnosed, contributing to the maintenance of the disease cycle and the increase in the morbimortality.[4-5] Therefore, it is important to improve the access to the health services, intensify the screening for the early detection of new cases and the immediate start of the treatment.

The effective treatment of childhood TB is paramount to halt the disease progression, to prevent unfavorable outcomes, and refrain the population from becoming reservoirs for the transmission of the disease. Besides that, the timely diagnosis of TB is a challenge for the health services since the symptoms are unspecific in the early stages of the disease in children. It is estimated that up to 50% of the cases can be asymptomatic in children.[6-7]

Childhood TB presents clinical specificities according to the age group. In children from five to 10 years old (school age), the predominant form is the bacillary or paucibacillary, while in children under the age of five, it is considered a sentinel event, reflecting the dissemination potential of the disease due to the contact with a bacillary adult patient.[7-9] Thus, it is very important to carry out a rigorous assessment and to adopt effective strategies for the detection and the prevention of new cases.[4]

Furthermore, it is necessary that the healthcare professionals, especially nurses, are aware of the risk factors increasing the probability of infection or progression from latent infection, or active disease in childhood TB. These factors are classified in three categories: 1) being born, or significant time spent in an endemic TB environment; 2) known exposure, or suspected TB, or high risk of exposure to TB; and 3) immunosupression.[6] The understanding and monitoring of these risk factors are essential for the development of interventions directed to the control of childhood TB, mainly in vulnerable groups.

Aiming to establish strategies for the containment and blocking the transmission of TB in the world, the World Health Organization (WHO) implemented the End TB strategy with the objective of developing measures to combat the disease, proposing an epidemiological elimination until the year 2035, with a reduction of 95% of the disease burden.[8] Thus, the End TB strategy alerts for the risk of infection in children, especially those living in the 30 countries with higher burden of TB; Brazil is among them.

In a national level, the National Plan for the End of TB as a public health problem in Brazil was stablished in 2017. Among the strategies implemented with regard to the prevention and promotion of childhood TB it is worth mentioning vaccination, precise diagnosis and treatment, treatment compliance, contact tracing, and transmission control measures.[9]

In this context, the development of the present study is of great relevance for the scientific community in the sense of assuring the thematic visibility, considering the circumstances of the disease in children. Moreover, it incorporates the temporal trend, which contributes to the understanding of childhood tuberculosis' behavior in a territory. Therefore, our objective is to analyze the temporal trend of TB in individuals under the age of 15 in the state of Paraná, according to the classification previously established by the TB Epidemiological Report 2023 (*Boletim Epidemiológico da TB* 2023).[3]

METHODS

This is an ecological study of temporal series.10 This study was carried out in the 399 municipalities from Paraná state, which is divided in four health macro-regions, named East (with 93 municipalities), West (94 municipalities), North (97 municipalities), and Northwest (115 municipalities) (Figure 1).

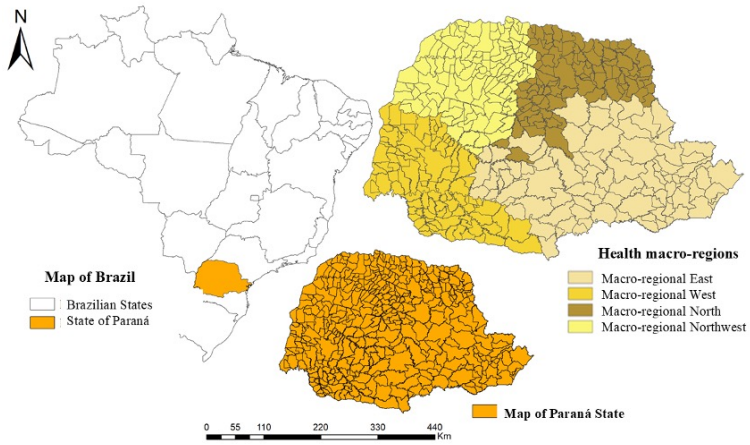

Figure 1. Map of the scenario in national, state and by health macro-region level. Bandeirantes – Paraná, 2023.

The territorial area of the state of Paraná is estimated to be 199,298,981 km², with a population of 11,444,380 people, from which 2,195,297 were under 14 years old, being 1,074,698 (55.8%) females, and 1,120,599 (44.2%) males, according to data from the Brazilian Institute of Geography and Statistics, 2022 (IBGE). The Human Development Index (HDI) for the year 2021 was 0.769, with an infant mortality rate of 9.46, and for those under five years old, 10.95.[10]

The study population included all confirmed childhood TB cases in the Notifiable Diseases Information System (*Sistema de Informação de Agravos de Notificação* - SINAN) from the Brazilian Ministry of Health, from 1 January 2013 to 31 December 2022.

Inclusion criteria used were patients under 15 years of age (up to 14 years, 11 months, and 29 days) at the time of diagnosis, both genders, and being a resident of the state of Paraná during the period of study. The cases with no information about the municipality of residency and those with change in diagnosis were excluded from the study. The child population was considered to include participants who corresponded to the age classifications pre-established by notification systems in Brazil, that is, children and adolescents aged from zero up to 14 years, 11 months, and 29 days, according to the terminology described in the TB Epidemiological Report 2023.[3]

Age group was considered the dependent variable, categorized as follows: under one year; one to four years; five to nine years; and 10 to 14 years. For data analysis, sociodemographic variables (sex, race/color, and area of residence) and clinical profile (type of entry, clinical form, laboratory confirmation, sputum bacilloscopy, and treatment outcome/closure status) were used. Laboratory confirmation was established by the combination of information available at the fields related to the case confirmation criteria "bacilloscopy" collected from the DATASUS/SINAN website.

The statistical analyses were divided into two stages. In the first, exploratory data analysis was conducted, including descriptive statistics and calculation of absolute and relative frequencies using *Statistical Package for the Social Sciences*® software. (SPSS) version 20.0.

In the second stage, time series analysis was applied, consisting of a set of continuous observations sequentially over time.[12] This method aims to classify the temporal trend of the event during the study period as increasing, decreasing, or stationary. The time series statistics were calculated using STATA version 14, applying the Prais-Winsten generalized linear regression method. This procedure corrects for first-order temporal autocorrelation in organized time series analyses. The annual variation in the measure and its 95% confidence intervals (CI 95%) were also calculated.[12]

The temporal trend analysis utilized the Prais-Winsten generalized linear regression model, considering as independent variables (X – sociodemographic and clinical) the years evaluated (2013 - 2022) and as dependent variables (Y – the cases of childhood TB according to the age group - under one year; one to four years; five to nine years; and 10 to 14 years). To reduce the heterogeneity of residual variances in the temporal regression analysis, a logarithmic transformation (log10) of the Y values was applied.[13]

Since this is a study based on public data (DATASUS/SINAN), available at http://tabnet.datasus.gov.br/cgi/tabcgi.exe?sinannet/cnv/tubercpr.def, there was no need for approval from the Research Ethics Committee with Human Beings, according to CNS Resolution No. 510 of 2016, which addresses research production and knowledge dissemination that are available without restriction to access by researchers and the general public.

RESULTS

During the period of study, 25,834 cases of TB were notified in the state of Paraná, from which 592 were childhood TB. As for the age group, 194 (32.8%) were 10 to 14 years old, 144 (24,3%) were under the age of one, 142 (24%) from one to four years of age, and 112

(18.9%) from five to nine years of age. Upon analyzing the sociodemographic characterization, there was a predominance of the male sex (66.7%), white race/color (64.6%) for those under 1 year of age, and urban residence (37.6%) for the age group between 10 and 14 years, 11 months, and 29 days (Table 1).

Table 1. Sociodemographic characterization of childhood TB, stratified by age group, Paraná state, from 2013 to 2022.

Variables	<1 year	1 to 4 years	5 to 9 years	10 to 14 years	Total
	N(%)	N(%)	N(%)	N(%)	N(%)
Sex					
Male	96 (66.7)	87 (61.3)	58 (51.8)	91 (46.9)	332 (56.1)
Female	48 (33.3)	55 (38.7)	54 (48.2)	103 (53.1)	260 (43.9)
Race/Color					
White	93 (64.6)	86 (60.6)	65 (58.0)	123 (63.4)	367 (62.0)
Mixed/Brown	28 (19.4)	39 (27.5)	39 (34.8)	56 (28.9)	162 (27.4)
Black	9 (6.3)	8 (5,6)	3 (2.7)	5 (2.6)	25 (4.2)
Asian/Yellow	2 (1.4)	-	-	2 (1.0)	4 (0.7)
Indigenous	1 (0.7)	2 (1.4)	4 (3.6)	2 (1.0)	9 (1.5)
Blank/No information	11 (7.6)	7 (4.9)	1 (0.9)	6 (3.1)	25 (4.2)
Area of Residence					
Urban	54 (37.5)	44 (31.0)	37 (33.0)	73 (37.6)	208 (35.1)
Rural	4 (2.8)	3 (2.1)	3 (2.7)	4 (2,1)	14 (2.4)
Peri-urban	-	2 (1.4)	-	2 (1.0)	4 (0.7)
Blank/No information	86 (59.7)	93 (63.5)	72 (64.3)	115 (59.3)	366 (61.8)

Among the analysed TB cases in individuals under 15 years of age, the majority of patients were classified as new cases (91.2%), with a higher proportion in the age group from 10 to 14 years old (92.8%). As for the clinical form, notified pulmonary (69.3%), with a higher proportion in children from one to four years of age (74.6%). Laboratory confirmation was obtained in 69.9% of cases. Confirmation was more frequent among children aged 10 to 14 years (38.1%) and those under one year of age (47.2%). For the variable "sputum bacilloscopy", the test was not performed in 51% of cases. Positivity was 25.3% for the age group 10 to 14 years and 27.8% for those under one year of age. As for the treatment outcome status, cure was the most frequent outcome (68.6%), reaching 81.4% in children from 10 to 14 years and 79.5% in children from five to nine years of age, followed by treatment interruption (4.1%) (Table 2).

Table 2. Clinical profile of childhood TB stratified by age group, Paraná state, from 2013 to 2022.

Variables	<1 year	1 to 4 years	5 to 9 years	10 to 14 years	Total
	N(%)	N(%)	N(%)	N(%)	N(%)
Type of Entry					
New case	128 (88.9)	130 (91.5)	102 (91.1)	180 (92.8)	540 (91.2)
Relapse	5 (3.5)	1 (0.7)	-	2 (1.0)	8 (1.4)
Re-entry after abandonment	4 (2.8)	6 (4.2)	5 (4.5)	2 (1.0)	17 (4.1)
Transfer	7 (4.9)	5 (3.5)	4 (3.6)	8 (4.1)	3 (0.5)
Clinical form					
Pulmonary	93 (64.6)	106 (74.6)	78 (69.6)	133 (68.6)	410 (69.3)
Extrapulmonary	30 (20.8)	29 (20.4)	31 (27.7)	53 (27.3)	143 (24.2)
Pulmonary + Extrapulmonary	21 (14.6)	6 (4.2)	3 (2.7)	8 (4.1)	38 (6.4)
Blank/No information	-	1 (0.7)	-	-	1 (0.2)
Laboratory confirmation					
With laboratory confirmation	68 (47.2)	19 (13.4)	17 (15.2)	74 (38.1)	178 (30.1)
Without laboratory confirmation	76 (52.8)	123 (86.6)	95 (84.8)	120 (61.9)	414 (69.9)
Sputum bacilloscopy					
Positive	40 (27.8)	8 (5.6)	9 (8.0)	49 (25.3)	106 (17.4)
Negative	30 (20.8)	31 (21.8)	34 (30.4)	45 (23.2)	140 (23.6)
Not done	60 (41.7)	89 (62.7)	59 (52.7)	94 (48.5)	302 (51.0)
Blank/No information	14 (31.8)	14 (31.8)	10 (22.7)	6 (13.6)	44 (7.4)

Variables	<1 year	1 to 4 years	5 to 9 years	10 to 14 years	Total
	N(%)	N(%)	N(%)	N(%)	N(%)
Treatment outcome status					
Cure	73 (50.7)	86 (60.6)	89 (79.5)	158 (81.4)	406 (68.6)
Treatment interruption	4 (2.8)	11 (7.7)	6 (5.4)	3 (1.5)	24 (4.1)
Death due to tuberculosis	5 (3.5)	1 (0.7)	1 (0.9)	1 (0.5)	8 (1.4)
Death from other causes	10 (6.9)	1 (0.7)	4 (3.6)	4 (2.1)	19 (3.2)
Transfer	33 (22.9)	21 (14.8)	6 (5.4)	119 (5.7)	79 (13.3)
Drug-resistant TB	2 (1.4)	-	1 (0.9)	3 (1.5)	6 (1.0)
Change of treatment regimen	2 (1.4)	2 (1.4)	1 (0.9)	-	5 (0.8)
Primary abandonment	-	3 (2.1)	1 (0.9)	-	4 (0.7)
Blank/No information	15 (10.4)	17 (12.0)	3 (2.7)	14 (7.2)	41 (6.9)

It is possible, based on *Prais-Winsten* regression, to conclude that the temporal trend was stationary for all variables under analysis (Table 3).

Table 3. Temporal trend of childhood TB stratified by age group, Paraná state, 2013 to 2022.

Variable	APC (CI 95%)	p-value	Trend
< 1 year of age	0.22(-0.08 – 0.53)	0.58	Stationary
1 to 4 years of age	0.27(-0.05 – 0.60)	0.10	Stationary
5 to 9 years of age	0.03(-0.23 – 0.31)	0.78	Stationary
10 to 14 years of age	-0.04(-0.33 – 0.25)	0.77	Stationary

Abbreviations: APC: Annual Percentage Change; CI: Confidence Interval.

Regarding the year of notification of childhood TB cases, in 2014 there was a decrease in the number of cases among individuals under one year of age (nine cases notified). In the other age groups, namely, one to four years old (17 cases) and 10 to 14 years old (23 cases), there was an increase. In 2020 it was observed an increase in the number of notifications (a total of 76 cases notified), followed by a decrease in 2016 and 2021 in all age groups (44 and 59 notifications, respectively) (Figure 2).

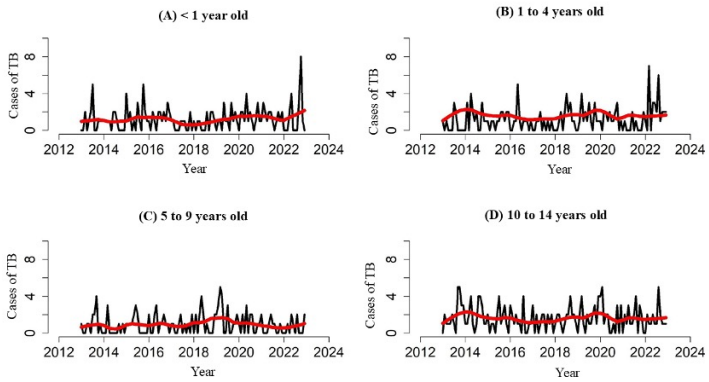

Figure 2. Temporal trend of childhood TB cases stratified by age group, Paraná state, from 2013 to 2022.

DISCUSSION

This study showed that childhood TB remained stationary in Paraná over the past ten years, when 32.77% (192) of childhood TB cases were reported in the 10 to 14 age group, and 24.32% (142 cases) occurred in children under one year old. This result is similar to findings observed in international studies, particularly among school-age children.[14-16]

Although Paraná state shows a stationary trend in childhood TB cases, there is an increase in the number of cases in the states of São Paulo, Rio de Janeiro, Pernambuco, and Amazonas, which represent 51.2% of the total cases in the national level.[3] A national study that analyzed cases notified between 2010 and 2021 showed that the highest rates were in the North and Central-West regions of the country.[17] In the state of Sergipe, the trend of childhood TB between 2001 and 2017 was stationary, as in the present study.[17]

By showing a stationary trend within the territory, it becomes evident that health services and the strategies adopted are insufficient, meaning they are maintaining a stagnation in the pathology's status. Therefore, there is a need to intensify health interventions and innovate and/or review the strategies being implemented by managers within health services.

Another factor that may be related to this stationary profile is the underreporting of childhood TB. Research carried out in Pakistan revealed that 78% of the childhood TB cases diagnosed in the country were not notified to the National TB Control Program.[18]

Seeking greater control and guidance, WHO published in 2006 the Guidance for National Tuberculosis Programmes on the Management of Childhood Tuberculosis in Children, the first guidelines in the world to approach childhood TB.[19]

Among the recommendations it is highlighted: the use of the molecular test Xpert MTB/RIF as the initial

diagnostic test; in children and adolescents aged 3 to 16 years with non severe TB - no suspicion or evidence of multidrug resistance- the medication treatment was shortened to a 4 month regimen (2 months of de isoniazid (H), rifampicin (R), pyrazinamide (Z) e ethambutol (E), followed by 2 months of isoniazid and rifampicin (2HRZE/2HR)); the inclusion of family-centered care models to promote a supportive and protective environment; prevention strategies with strengthened contact investigation and TB screening, emphasizing prevention in vulnerable populations, including those living with HIV.[19]

The Ministry of Health also outlines key commitments, including training professionals to use the SINAN system, encouraging active case finding of individuals with respiratory symptoms, and promoting the evaluation of contacts of individuals with laboratory-confirmed TB for signs and symptoms of the disease, particularly in primary health care services, which serve as the gateway to the SUS (the Brazilian Unified Health System).[9]

The government of the state of Paraná aligns itself with the recommendations and strategies adopted by the Ministry of Health and, in 2022, launched the State Plan to End Tuberculosis as a Public Health Problem in Paraná, 2022-2030, which establishes the state's main commitments to combating TB and childhood TB.[20] It is worth noting that, among the recommendations of the State Plan for the End of TB, no specific strategies are mentioned for the child population, except for the indication of drug treatment, which highlights the invisibility of the issue in government spheres.

Therefore, childhood TB is a priority health issue that deserves the attention of policymakers and healthcare professionals, as children and adolescents are in a vulnerable situation considering that most infections occur through transmission from family members or other close contacts with TB.[5] Children under five years old represent an important demographic group that deserves attention from health services, as their primary or latent progression to active TB occurs rapidly, and severe manifestations of the disease are more common in this age group.[4]

In this regard, health services, particularly in primary health care, should prioritize case screening, diagnostic clarification, and effective management of directly observed treatment, as well as the inclusion of home visits to identify social determinants of health and assess risk classification.[21]

The implementation of home visits contributes to the screening and early identification of undiagnosed new cases, preventing their progression. A study conducted in The Gambia involving 4,042 children under the age of 15, screened through home visits, found that 1.6% had TB, with 40% of these cases being asymptomatic.[22] Therefore, healthcare workers must be prepared and trained to identify signs, symptoms, and risk factors, and to implement targeted strategies for appropriate and early screening during routine visits.

However, the detection of childhood TB in health services is a challenge, as the clinical presentation of the disease is similar to other common findings in childhood, such as pneumonia, viral and bacterial bloodstream infections, and malnutrition. Therefore, primary healthcare professionals must be trained in early diagnosis and the development of new tools, not solely based on sputum, that enable rapid and reliable identification of childhood TB.

The diagnosis and treatment of childhood TB present significant challenges, particularly in large and expansive territories such as the state of Paraná, due to resource limitations and the population's access to health services. A study conducted in Cambodia identified several key barriers to accessing childhood TB services, such as lack of knowledge and awareness about the disease, costs involved, time limitation and issues related to the cultural aspects associated to the disease, and the obstacles to accessing specialized health services.[24]

Upon analyzing the trend of childhood TB cases, a decline is observed in 2014, a factor that may be associated with the implementation of the National Health Promotion Policy, which led to intensified training of healthcare professionals in infectious diseases in the state of Paraná.[9]

Over recent decades, literature has consistently highlighted improvements in health indicators in Brazil, particularly concerning child health. These advancements are closely linked to the implementation of public health policies at the national level, such as the establishment of the *Rede Cegonha* (Stork Network). The *Rede Cegonha* focuses on maternal and child health, offering a model of care that spans from prenatal care to the child's second year of life.[25]

Another policy that complements the fight against childhood TB is the National Policy for Comprehensive Health Care for Adolescents (*Política Nacional de Atenção Integral à Saúde do Adolescente*) alongside the Program Protect and Health Care for Adolescents in the Primary Care (*Proteger e Cuidar da Saúde de Adolescentes na Atenção Básica*), aimed at promoting, protecting, and recovering health. However, it is emphasized that these policies also do not describe specific aspects regarding the approach to childhood TB, thus once again highlighting the invisibility of policies and strategies directed at TB in the child population.[26]

The initiative has proven significant, reflecting not only in the quality of care but also in the reduction of infant mortality, contributing to an estimated decline of approximately 4.5%, which aligns with the findings of this study, where only 1.4% of cases progressed to death

from TB, and 3.2% to death from other infectious diseases. Furthermore, the expansion of the Family Health Strategy (*Estratégia de Saúde da Família* - ESF) through the inclusion and involvement of Community Health Agents played a crucial role in this progress, strengthening healthcare services at this level and enabling a positive impact on health indicators of the population, especially children.[25]

Moreover, the healthcare service, through the Unified Health System (SUS) and the National Immunization Program, provides specific services that assist in the prevention of TB development, such as vaccination. The administration of the Bacillus Calmette–Guérin (BCG) vaccine prevents severe cases and progression to death from TB; it should be administered during the neonatal period.[9] Therefore, it is necessary to implement screening within primary health care services along with increasing BCG vaccination coverage in children under five years of age, since they are more susceptible to severe forms of TB, and vaccination remains an important strategy to reduce both severe cases and mortality in this age group.[3]

Therefore, healthcare services at the primary health care level play a crucial role in the eradication of TB by ensuring early diagnosis and timely initiation of treatment, conducting directly observed treatment to promote adherence to the appropriate therapeutic regimen, thereby preventing unfavorable outcomes such as treatment interruption, development of drug-resistant TB, and death from TB.[8]

Despite the results being relevant and due to a limited number of studies addressing the topic in the child population, there were some limitations, such as the use of secondary data, which may have introduced bias to the research due to the possibility of underreporting of cases.

The study advances knowledge by highlighting the temporal trend of TB in children under 14 years, 11 months, and 29 days, particularly in a context where there is a lack of studies. The results indicate a stationary trend of childhood TB in Paraná state, highlighting the importance of expanding strategies to combat TB in healthcare services for timely detection, diagnosis, and appropriate treatment of cases, including the implementation of directly observed treatment (DOT), as the stationary trend suggests the persistence of the disease in the region. It is also emphasized the importance of promoting the expansion of training for healthcare professionals regarding the clinical and epidemiological approach to the disease in children under 15 years, with an emphasis on contact tracing and the use of diagnostic technologies.

Besides that, it is necessary to enhance information and surveillance systems, with improved quality of data notified, enabling continuous monitoring that is sensitive to changes in the disease's epidemiological profile. The need for educational and intersectoral campaigns aimed at the population is also highlighted, focusing on raising awareness about the signs and symptoms of childhood TB, as well as treatment adherence, and the implementation of information technologies in monitoring, such as teleconsultation.

Finally, it is suggested to develop new studies with analytical and qualitative approaches that allow a deeper understanding of the factors associated with the persistence of childhood TB in the territory, supporting more effective public policies tailored to the local reality.

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AUTHORS' CONTRIBUTIONS

Alessandro Rolim Scholze contributed to project management, writing of the abstract, introduction, methodology, discussion, interpretation and description of results, table preparation, conclusions, revision, and statistics. **Camila da Cruz Rodrigues** contributed to the literature review, introduction, results description, table preparation, and conclusions. **Kelly Holanda Prezotto** contributed to the interpretation of results, conclusions, revision, and statistics. **Carolina Fordellone Rosa Cruz** contributed to the writing of the abstract, introduction, methodology, discussion, interpretation and description of results, conclusions, and revision. **Josilene Dália Alves** contributed to the writing of the abstract, introduction, methodology, discussion, interpretation and description of results, table preparation, conclusions, revision, and statistics. **Leonardo Bigolin Jantsch** contributed to the writing of the abstract, introduction, methodology, discussion, interpretation and description of results, table preparation, conclusions, revision, and statistics. **Rosana Rosseto de Oliveira** contributed to the writing of the abstract, introduction, methodology, discussion, interpretation and description of results, revision, and statistics. **Flavia Meneguetti Pieri** contributed to the writing of the abstract, introduction, methodology, discussion, interpretation and description of results, and revision. **Emiliana Cristina Melo** contributed to project management, writing of the abstract, introduction, methodology, discussion, interpretation and description of results, table preparation, conclusions, revision, and statistics.

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

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Review Article

Infection in ICU patients treated in the intensive care unit based on nursing and medical measures

Infecção em pacientes internados em UTI em unidade de terapia intensiva com base em medidas de enfermagem e médicas

Infección en pacientes de UCI tratados en la unidad de cuidados intensivos según medidas médicas y de enfermería

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Corresponding author:
E-mail: m88mesgarian@gmail.com
Address: Faculty of medicine, Tehran medical sciences, Islamic Azad University, Tehran, Iran.

Nahid Mirzaei-Triabadi[1]
Maryam Roham[2]
Masoume Mesgarian[3]

[1]Department of Infection disease and Tropical medicine, school of medicine, Shahid Motahari Burns Hospital, Iran University of medical sciences, Tehran, Iran.
[2]Infectious disease specialist, school of medicine, Iran University of Medical Sciences, Tehran, Iran.
[3]Department of infection disease, Faculty of medicine, Tehran medical sciences, Islamic Azad University, Tehran, Iran.

ABSTRACT

Background and Objectives: Irritable bowel syndrome (IBS) is a common gastrointestinal disorder characterized by symptoms such as diarrhea, constipation, abdominal pain, stress, chronic fatigue, and bloating. This study investigates the prevalence of infection in patients treated in the intensive care unit (ICU), focusing on nursing and medical measures. **Methods:** The present study conducted a systematic review of 40 articles published between 2012 and 2024, utilizing keywords such as "ICU," "Nursing," "Medical Staff," "Health Care" and "Hospital Infection" in databases including PubMed, Web of Science, Scopus, Science Direct, EBSCO, Wiley, Elsevier, Embase, and Google Scholar. **Results:** The findings indicate that urinary tract infections are the most common, while pneumonia is the deadliest hospital-acquired infection. In some centers, however, nosocomial infections of the circulatory system are the main cause of patient mortality. The meta-analysis revealed a prevalence of infection among ICU patients of 82%. **Conclusion:** Given the high prevalence of hospital-acquired infections, effective nursing and medical care are essential for reducing these infections.

Keywords: *Infection. Delivery of Health Care. Treatment Staff. Nurses. Intensive Care Units.*

RESUMO

Justificativa e Objetivos: A síndrome do intestino irritável (SII) é um distúrbio gastrointestinal comum, caracterizado por sintomas como diarreia, constipação, dor abdominal, estresse, fadiga crônica e distensão abdominal. Este estudo investiga a prevalência de infecção em pacientes tratados em unidade de terapia intensiva (UTI), com foco em medidas de enfermagem e médicas. **Métodos:** O presente estudo realizou uma revisão sistemática de 40 artigos publicados entre 2012 e 2024, utilizando palavras-chave como "UTI", "Enfermagem", "Equipe Médica", "Assistência Médica" e "Infecção Hospitalar" em bases de dados como PubMed, Web of Science, Scopus, Science Direct, EBSCO, Wiley, Elsevier, Embase e Google Acadêmico. **Resultados:** Os achados indicam que as infecções do trato urinário são as mais comuns, enquanto a pneumonia é a infecção hospitalar mais letal. Em alguns centros, no entanto, as infecções nosocomiais do sistema circulatório são a principal causa de mortalidade dos pacientes. A meta-análise revelou uma prevalência de infecção entre pacientes de UTI de 82%. **Conclusão:** Dada a alta prevalência de infecções hospitalares, cuidados médicos e de enfermagem eficazes são essenciais para reduzir essas infecções.

Descritores: *Infecção. Prestação de Cuidados de Saúde. Equipe de Tratamento. Enfermeiros. Unidades de Terapia Intensiva.*

RESUMEN

Justificación y Objetivos: El síndrome del intestino irritable (SII) es un trastorno gastrointestinal común que se caracteriza por síntomas como diarrea, estreñimiento, dolor abdominal, estrés, fatiga crónica y distensión abdominal. Este estudio investiga la prevalencia de infecciones en pacientes tratados en la unidad de cuidados intensivos (UCI), centrándose en las medidas médicas y de enfermería. **Métodos:** El presente estudio realizó una revisión sistemática de 40 artículos publicados entre 2012 y 2024, utilizando palabras clave como "UCI", "Enfermería", "Personal médico", "Atención sanitaria" e "Infección hospitalaria" en bases de datos como PubMed, Web of Science, Scopus, Science Direct, EBSCO, Wiley, Elsevier, Embase y Google Scholar. **Resultados:** Los hallazgos indican que las infecciones del tracto urinario son las más comunes, mientras que la neumonía es la infección intrahospitalaria más mortal. Sin embargo, en algunos centros, las infecciones nosocomiales del sistema circulatorio son la principal causa de mortalidad. El metanálisis reveló una prevalencia de infección del 82% entre los pacientes de la UCI. **Conclusión:** Dada la alta prevalencia de infecciones intrahospitalarias, la atención médica y de enfermería eficaz es esencial para reducirlas.

Palabras Clave: *Infección. Atención Sanitaria. Personal de Tratamiento. Enfermería. Unidades de Cuidados Intensivos.*

INTRODUCTION

Patients in the intensive care unit (ICU) are frequently at risk for infections, which can lead to sepsis.[1] Despite numerous studies providing national and international epidemiological data on sepsis since 2009, fewer studies have focused exclusively on the underlying infections.[1] Detailed data on infection types, including causative microorganisms and the availability of diagnostic and treatment options, is crucial for raising awareness among clinicians, patients, and caregivers regarding the consequences of infections.[2–3] Understanding infection risk factors can assist in developing targeted policies for diagnosis and treatment, facilitate appropriate resource allocation, support the design of interventional studies, and provide a benchmark for evaluating advancements in patient outcomes and the effectiveness of novel therapies over time.[4–6]

Research indicates that 45% of patients have suspected or confirmed infections, with 62% receiving antibiotics.[7–8] Additionally, studies report that 71% of patients received prophylactic or therapeutic antibiotics, and 51% had a suspected or confirmed infection.[8–9]

Considering the significance of infection spread, the global rate of hospital mortality, and the roles of nurses and doctors, the current study investigates the percentage of infections in patients treated in the ICU, focusing on nursing and medical measures.

METHODS

This systematic review and meta-analysis examined 40 articles published between 2012 and 2024. Keywords such as “ICU,” “Nursing,” “Medical Staff”, “Health Care,” and “Hospital Infection” were used to search international databases including PubMed, Web of Science, Scopus, Science Direct, EBSCO, Wiley, Elsevier, Embase, and Google Scholar, following the PRISMA 2020 27-item checklist. Two researchers independently collected data using a standardized data collection form designed to minimize reporting errors and omissions. The form included the following information: author name, year of publication, infection status in patients, number of participants, age range, irrigation technique, etiology, and medications.

Inclusion Criteria

Studies were selected based on the PICO framework. The population (P) included patients treated in the ICU; the intervention (I) involved nursing interventions; comparators (C) included no specific interventions or routine care; and outcomes (O) focused on infection prevalence. Eligible studies included randomized controlled trials (RCTs), cohort studies, case-control studies, and comparative studies published between January 2012 and December 2024.

Exclusion Criteria

Studies were excluded if they were non-research articles, such as editorials, commentaries, letters to the editor, or case reports. Research not directly related to accelerating recovery in ICU patients, such as studies focused on unrelated surgical interventions or non-clinical outcomes, was also excluded. Additionally, studies that did not report specific clinical outcomes related to recovery in ICU patients or those published in languages other than English were excluded.

The prevalence of infection in patients based on nursing and medical measures was calculated using a fixed-effect model and the inverse-variance method, with $p<0.05$ considered significant.

RESULTS

The present study utilized the PRISMA 2020 flow diagram for study selection, which is reported as a standard in PRISMA 2020.

The initial search identified 40 articles. In the first phase, one article was eliminated due to duplicate records based on article titles. In the second step, studies that did not meet the inclusion criteria were excluded by reviewing the abstracts of 39 articles (n = 6). In the third step, four articles with incomplete data or non-compliance with the inclusion and exclusion criteria were eliminated after examining the full texts of 35 articles. Ultimately, seven articles were included in the present study (Figure 1 and Table 1).

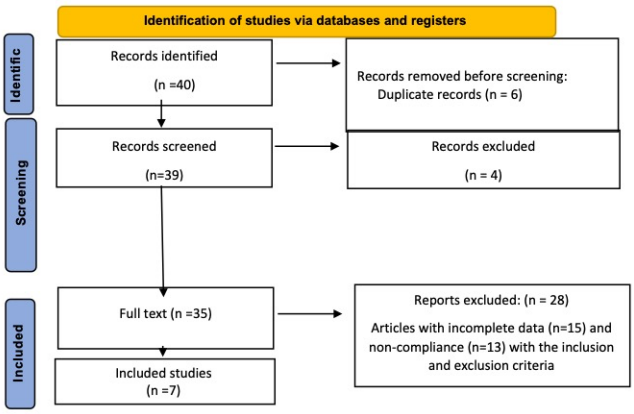

Figure 1. PRISMA 2020 flow diagram.

The prevalence of infection among ICU patients was found to be 82% [ES: 0.82, 95% CI; 0.78–0.97]. The proportion of patients with suspected or confirmed infections ranged from 78% to 97% (Table 1).

Table 1. Data from selected articles in the present study.

Raw	Study	Year	Proportion	Weight 98%	Weight %
1	Otaghvar et al.[10]	2023	0.64	[0.11–1.72]	3.02
2	Fazaeli et al.[11]	2020	0.52	[0.42–2.11]	4.00
3	Fathi et al.[12]	2020	0.96	[0.44–1.02]	6.32
4	Gazerani et al.[13]	2015	0.65	[0.25–0.98]	5.12
Heterogeneity $t^2 = 0.00$, $I^2 = 0.00$, $H^2 = 0.9$			0.55	[0.34–0.58]	1.23
Test of $\Theta = \Theta$, Q (4) = 3.45, P = 0.77					
1	Malekzadeh et al.[14]	2021	0.56	[0.11–0.66]	1.55
2	Mehrabian et al.[15]	2014	0.66	[0.15–0.48]	4.33
3	Yavari et al.[16]	2015	0.48	[0.190.55]	6.77
Heterogeneity $t^2 = 0.05$, $I^2 = 0.07$, $H^2 = 0.78$			0.82	[0.78–0.97]	
Test of $\Theta = \Theta$, Q (4) = 3.01, P = 0.11					

DISCUSSION

Research indicates that the elderly are more likely to acquire hospital infections due to immune system deficiencies, diabetes, and vitamin deficiencies. Typically, elderly patients and those with urinary catheters exhibit symptoms of urinary infections, including behavioral changes such as agitation, uncontrollable urination, fever and chills, and intense burning sensation and redness at the catheter site.[17] Children are also at increased risk for hospital infection due to their immature immune system.[18] Patients in the ICU are particularly vulnerable to nosocomial infections; the use of artificial ventilation devices and the presence of various intravenous and urinary catheters contribute to the number of both resistant and sensitive microorganisms, necessitating vigilant nursing and medical measures. Furthermore, prolonged antibiotic use increases the risk of infections.[19]

Despite the implementation of numerous nursing and medical protocols to prevent surgical site infections, reports indicate a 1% to 3% chance of acquiring a hospital-acquired infection.[20] Findings from one study demonstrated that after nursing care, the overall rate of surgical site infections decreased from 3.3% to 1.8%.[21]

Statistics show that women are 50% more susceptible to urinary tract infections (UTIs) than men, attributed to anatomical differences in urinary tracts. UTIs can be painful and, if left untreated, may lead to serious complications, including kidney infections and sepsis. Common symptoms include a strong urge to urinate and pain or burning during urination. Most UTIs are caused by bacteria, though in some cases, they may result from fungal proliferation or, rarely, viral infections. While antibiotics are commonly prescribed to treat various types of UTIs, individuals can also take preventive measures to reduce their risk. If left untreated, the infection may spread to the bloodstream and lead to sepsis—a life-threatening condition, particularly when the upper urinary tract is involved.[22] With regard to ciprofloxacin, it is generally not recommended for uncomplicated UTIs, as the potential risks often outweigh the benefits in such cases. However, in instances of complicated UTIs or kidney infections where alternative treatment options are unavailable, a doctor may consider prescribing ciprofloxacin.[23–24,27]

Infection following breast prosthesis surgery is a significant complication.[25–27,28] If symptoms of infection are not promptly addressed, the infection may enter the bloodstream, leading to complex treatment processes and potentially fatal outcomes. Therefore, it is crucial to take infections following breast prosthesis surgery seriously.[29]

It is believed that implementing a safety management system can help care department managers identify failures in the service delivery before they occur, in collaboration with human resources and utilizing active tools such as failure mode and effects analysis.[30] Adhering to functional area standards in the ICU can reduce infection rates.[31]

ICUs in low-income countries face substantial challenges, including a shortage of healthcare workers and inadequate infrastructure.[32–34] Studies also show that the nurse-to-patient ratio in Brazilian hospitals is suboptimal, and the number of nurses in ICUs significantly impacts patient clinical outcomes. Therefore, it is recommended to develop specialized care units with a focus on strengthening human resources.[35]

The performance of ICUs in controlling hospital infections requires increased attention and effort. To enhance ICU quality, it is essential to further improve intensive care units, requires proper documentation of actions taken by nurses and doctors. Hospitals can improve service quality by accurately recording patient information, medications used, and length of stay through software systems.[36]

Infections in cancer patients can be caused by bacteria, viruses, fungi, or protozoa and may become more severe, posing life-threatening risks. Patients should seek medical attention if they experience fever, redness, swelling, weakness, or other signs of infection, as early

treatment is crucial for effective management. Some infections can be prevented through vaccination. Recent advancements in cancer treatment have significantly improved outcomes for many patients. Maintaining a healthy diet, engaging in recommended exercise, and practicing good hygiene may help reduce the risk of infection. Limitations of the present study include the small sample sizes and variability in methodologies and instruments used in the reviewed studies. Future clinical trials are recommended to evaluate the outcomes of nursing and medical interventions over extended follow-up periods to control infections.

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AUTHORS' CONTRIBUTIONS

Nahid Mirzaei-Triabadi was responsible for conducting the literature search and writing the abstract, introduction, and methodology sections. **Maryam Roham** was responsible for writing the discussion, interpreting and describing the results, and preparing the tables. **Masoume Mesgarian** was responsible for preparing the conclusions, reviewing the manuscript, and conducting the statistical analyses.

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

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Review Article

Exposure to HIV during pregnancy and child neuropsychomotor development: a scoping review

Exposição ao HIV durante a gestação e o desenvolvimento neuropsicomotor infantil: uma revisão de escopo
Exposición al VIH durante la gestación y el desarrollo neuropsicomotor infantil: una revisión de alcance

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Corresponding author:
E-mail: raphaelabgg@academico.com.br
Address: Governor Marcelo Déda Avenue, 13, Downtown, Lagarto, Sergipe, Brazil.

Raphaela Barroso Guedes-Granzotti[1]
Matheus do Nascimentos Alves[2]
Lara Suzana de Oliveira Nunes[3]
Nathália Monteiro Santos[4]
Vinicius Nunes Araujo[3]
Carla Patrícia Hernandez Alves Ribeiro César[3]
Kelly da Silva[2]

[1]Graduate Program in Applied Health Sciences, Federal University of Sergipe, Lagarto, Sergipe, Brazil.
[2]Department of Speech-Language Pathology, Federal University of Sergipe, Lagarto, Sergipe, Brazil.
[3]Department of Speech-Language Pathology, Federal University of Sergipe, São Cristóvão, Sergipe, Brazil.
[4]Graduate Program in Applied Health Sciences, Federal University of Sergipe, Lagarto, Sergipe, Brazil.

ABSTRACT

Background and Objectives: Aiming to contribute to the elucidation of factors involved in neurodevelopmental alterations in children, whether infected or not, born to HIV-positive mothers, this study mapped the existing literature on the influence of HIV exposure during pregnancy on child neuropsychomotor development. **Methods:** This study is a scoping review registered on the Open Science Framework platform. An electronic search was conducted in the databases SciELO, PubMed, Embase, LILACS, Web of Science, CINAHL, BDTD, and the Open Gray repository, using descriptors related to child development and HIV. Additionally, a methodological quality assessment was performed. **Conclusion:** The analyzed studies indicate that HIV exposure during pregnancy is not a determinant of neuropsychomotor developmental alterations. Instead, HIV infection itself appears to be the critical factor due to the virus's impact on the central nervous system. Nevertheless, children exposed to HIV in utero but not infected may also experience developmental alterations, primarily influenced by environmental factors.

Keywords: *HIV. Acquired Immunodeficiency Syndrome. Child. Child Development.*

RESUMO

Justificativa e Objetivos: Visando contribuir para a elucidação dos fatores envolvidos nas alterações do neurodesenvolvimento de crianças, infectadas ou não, filhas de mães soropositivas para o HIV, este trabalho mapeou a literatura existente sobre a influência da exposição ao HIV durante a gestação no desenvolvimento neuropsicomotor infantil. **Método:** Revisão de escopo registrada na plataforma *Open Science Framework*. Foi realizada uma busca eletrônica nas bases de dados Scielo, PubMed, Embase, Lilacs, Web of Science, CINAHL, BDTD e no repositório *Open Gray* com descritores relacionados ao desenvolvimento infantil e ao HIV. Também foi realizada uma análise da qualidade metodológica. **Conclusão:** Os estudos analisados demonstraram que a exposição ao HIV durante a gestação não é determinante para alterações no desenvolvimento neuropsicomotor, e sim a própria infecção pelo HIV em virtude da ação do vírus no sistema nervoso central. Entretanto, crianças expostas ao HIV durante a gestação, mas não infectadas, também podem apresentar alterações do desenvolvimento, associadas principalmente a fatores ambientais.

Descritores: *HIV. Síndrome da Imunodeficiência Adquirida. Criança. Desenvolvimento Infantil.*

RESUMEN

Justificativa y Objetivos: Con el objetivo de contribuir a la elucidación de los factores involucrados en las alteraciones del neurodesarrollo en niños, ya sean infectados o no, nacidos de madres VIH positivas, este estudio realizó un mapeo de la literatura existente sobre la influencia de la exposición al VIH durante la gestación en el desarrollo neuropsicomotor infantil. **Método:** Se trata de una revisión de alcance registrada en la plataforma *Open Science Framework*. Se llevó a cabo una búsqueda electrónica en las bases de datos SciELO, PubMed, Embase, LILACS, Web of Science, CINAHL, BDTD y en el repositorio *Open Gray*, utilizando descriptores relacionados con el desarrollo infantil y el VIH. Además, se realizó un análisis de la calidad metodológica de los estudios incluidos. **Conclusión:** Los estudios analizados indican que la exposición al VIH durante la gestación no es un factor determinante en las alteraciones del desarrollo neuropsicomotor. En cambio, la infección por VIH en sí misma parece ser el elemento clave, debido a la acción del virus en el sistema nervioso central. No obstante, los niños expuestos al VIH en el período prenatal, pero no infectados, también pueden presentar alteraciones en el desarrollo, principalmente asociadas a factores ambientales.

Palabras Clave: *VIH. Síndrome de Inmunodeficiencia Adquirida. Niño. Desarrollo Infantil.*

INTRODUCTION

Childhood represents a fundamental stage of human development, as it is during this period that most neuropsychomotor development (NPMD) occurs. This process involves multiple aspects, including growth, neurological maturation, and the acquisition of behavioral, cognitive, and socio-emotional skills by the child. Several factors can influence neuropsychomotor development and are classified as intrinsic, when related to biological and genetic aspects, or extrinsic, when resulting from the environment in which the child is raised. Among the extrinsic factors, social and emotional aspects, maternal education level, family structure, and exclusive breastfeeding, among others, stand out.[8] In this way, child development results from processes involving complex neural pathways, which are susceptible to environmental, social, and potential pathological influences.[1,2]

Studies report that neurodevelopmental alterations in children infected with HIV are mainly due to the direct action of the virus on the central nervous system, given its neurotropism, but also to contributing factors related to maternal Aids (e.g., stage of the mother's illness, presence of opportunistic infections, nutritional status, among others), in addition to the use of alcohol and drugs during pregnancy, which can lead to prematurity, low birth weight, and longer hospitalization after birth. As well as socioeconomic conditions, such as the physical environment and unfavorable caregiving practices, including violence, orphanhood, lack of access to healthcare, social vulnerability, low educational level, and limited parental knowledge about child development.[3–6]

With the widespread access of pregnant women to antiretroviral therapy (ART), the number of children exposed to HIV during pregnancy but not infected has been increasing, and despite being limited, studies have also indicated neurodevelopmental alterations in these children.[7,8] However, the literature remains unclear regarding the prevalence of neurodevelopmental alterations when comparing HIV-exposed but uninfected children (HEU), HIV-exposed and infected children (HEI), and HIV-unexposed and uninfected children (HUU).

In this context and aiming to contribute to the elucidation of factors involved in neurodevelopmental alterations in children—whether infected or not—born to HIV-positive mothers, this study seeks to compile scientific literature on the topic, identify gaps, and systematically understand the main findings. Thus, the objective of this study was to map the existing literature on the influence of HIV exposure during pregnancy on child neuropsychomotor development.

METHODS

The present study follows a scoping review design and adhered to the recommendations of PRISMA-ScR and the Joanna Briggs Institute Manual for Evidence Synthesis for Scoping Reviews. The study was registered on the Open Science Framework (OSF) platform (10.17605/OSF.IO/3X69R).[9,10]

To address the research question and develop the eligibility criteria, the PCC strategy was used, where the Population refers to children aged zero to six years; the Concept, to neuropsychomotor development; and the Context, to children born to HIV-positive mothers during pregnancy. Thus, the guiding question was: “Do children aged zero to six years, born to HIV-positive mothers during pregnancy, present delays in neuropsychomotor development?”

The searches were conducted in PubMed, Embase, SciELO, LILACS, the Brazilian Digital Library of Theses and Dissertations (*Biblioteca Digital Brasileira de Teses e Dissertações* - BDTD), Web of Science, CINAHL, and OpenGrey on December 17, 2022, with no language restrictions, using the following strategy adapted for each database: ((Infant OR Child OR "Preschool Children") AND (HIV OR Aids OR "Human Immunodeficiency Virus" OR "Aids Virus" OR "HIV Infection") AND ("Child Development" OR "Infant Development" OR "Development, Infant" OR "Developmental Disabilities" OR "Disabilities, Developmental" OR "Developmental Disability" OR "Child Development Disorder" OR "Developmental Delay Disorders" OR "Child Development Deviations" OR "Child Development Deviation")).

The selection stage was carried out using the Rayyan tool by two blinded reviewers, through the reading of the title and abstract. In cases of discrepancies between the reviewers, a third reviewer was consulted. Subsequently, the texts were read in full, applying the following inclusion criteria: observational studies (cross-sectional and cohort), involving children aged between zero and six years, that assessed some domain of neuropsychomotor development and confirmed maternal HIV seropositivity during pregnancy.

For the extraction of results from the eligible studies, a data extraction spreadsheet was designed by the third reviewer and validated by the two reviewers. The results were individually extracted by the two reviewers and then compared and unified by the third reviewer. Possible discrepancies were resolved through consensus meetings, led by the third reviewer. The data extracted from the selected studies included the authors' names, year of publication, country where the research was conducted, sample characteristics, the tests or types of neurodevelopmental assessment used, and the main findings. The results were presented narratively in the text and through tables.

The methodological quality assessment was carried out by two reviewers, and in cases of discrepancies, a third reviewer was consulted. The research protocols from The Joanna Briggs Institute (10.46658/JBIMES-24-09) were used, specifically the Checklist for Analytical Cross Sectional Studies, consisting of eight questions, and the Checklist for Cohort Studies, consisting of eleven questions. In the final scoring of the Checklist for Analytical Cross Sectional Studies, the risk of bias can be considered high for studies that received up to 49% of the responses marked as "yes" (0 to 3.92), moderate when the study received 50% to 69% (4 to 5.52), and low when the study received more than 70% of the responses marked as "yes" (6.4 to 8 points). In the final scoring of the Checklist for Cohort Studies, the risk of bias can be considered high for studies that received up to 49% (0 to 5.39) of the responses marked as "yes," moderate when the study received 50% to 69% (5.5 to 7.59), and low when the study received more than 70% (7.7) of the responses marked as "yes".[10]

RESULTS E DISCUSSION

After the database search, 4,625 articles were found, with 682 duplicates removed. After exclusion based on title and abstract screening, 166 articles remained for full-text reading, of which 73 were selected (Figure 1).

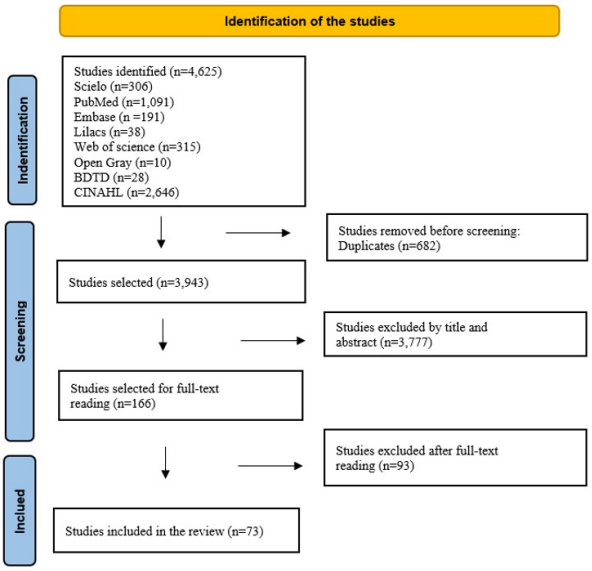

Figure 1. Flowchart of article search and selection.

The oldest study was from 1992 and the most recent from 2021. The studies were conducted on three continents — America, Africa, and Asia — in 20 different countries: South Africa,[12–31] Botswana,[32–35] Brazil,[36–39] Canada,[40–42] Colombia,[43] China,[44] United States,[45–50] United States and Puerto Rico,[51–55] Haiti,[56] India,[57] Iran,[58,59] Malawi,[60] Kenia,[61–64] Democratic Republic of the Congo,[65] Rwanda,[65] Thailand,[66,67] Tanzania,[68,69] Uganda,[11,70–75] Zaire, currently the Democratic Republic of the Congo,[76] Zâmbia,[76] Zimbabwe,[77–80]. Puerto Rico was counted as a country because it is an unincorporated territory of the United States, and Zaire was counted as Congo (Frame 1).

Frame 1. Articles included in the review.

Author (year)	Place	Sample	Protocols	Main Results
Aylward et al. (1992)[81]	United States	96 HEI = 12 HEU = 39 HUU = 45	BSID	Children in the HEI group showed significantly poorer performance in NPMD compared to children in the HEU and HUU groups.
Msellati et al. (1993)[67]	Rwanda	436 HEI = 50 HEU = 168 HUU = 218	Own Protocol	Children in the HEI group exhibited developmental delays more frequently than those in the HEU and HUU groups, with the delays being associated with the stage of Aids.
Chase et al. (1995)[45]	United States	51 HEI = 24 HEU = 27	BSID	The children were assessed at two time points. Motor delay was significantly worse in the HEI group at both time points, and cognitive delay was significantly worse in the HEI group at the second time point. Thus, early and persistent motor developmental delay, along with cognitive developmental deceleration, distinguish HEI from HEU.
Boivin et al. (1995)[76]	Zaire (Congo)	50 HEI = 14 HEU = 20 HUU = 16	ECSP and DDST	Children in the HEI group have significant deficits in NPMD compared to children in the HEU and HUU groups
Gay et al. (1995)[56]	Haiti	126 HEI = 28 HEU = 98	BSID	Over the first 24 months of life, the average developmental rate of infants in the HEI group is significantly slower than that of infants in the HEU group, with differences between the groups increasing over time.
Pollack et al. (1996)[49]	United States	91 HEI = 22 HEU = 42 HUU = 27	BSID	The delay in the NPMD for the HEI group, compared to the other groups, was first observed at 12 months and was correlated with the increase in viral load. It suggests that early intervention with potent antiretroviral agents aimed at reducing HIV viral load may mitigate the effects of HIV on growth and NPMD.
Drotar et al. (1999)[70]	Uganda	410 HEI = 61 HEU = 234 HUU = 115	BSID	The infants in the HEI group showed poorer performance on motor and cognitive assessments and experienced greater developmental deceleration compared to infants in the HEU and HUU groups.
Knight et al. (2000) [48]	United States	45 HEI = 20 HEU = 25	BSID	Infants in the HEI group had significantly lower BSID scores at baseline (cognitive development) and at follow-up (motor development) compared with those in the HEU group. When HIV infection and neurological deficits were considered together, HIV-positive children with neurological deficits scored significantly lower than HIV-positive children without neurological deficits and those in the HEU group, with and without neurological diagnoses. It suggests that CNS involvement is a critical pathway through which HIV affects the neurodevelopment of infants.
Chase et al. (2000)[55]	United States and Puerto Rico	595 HEI = 114 HEU = 481	BSID	A significant proportion of HEI children showed early cognitive and motor delay or decline, which may be important indicators for monitoring the early progression of HIV.
Smith et al. (2000)[54]	United States and Puerto Rico	114 HEI = 114	BSID	Early HIV infection increases the risk of developmental impairment during the first 30 months of life.

Author (year)	Place	Sample	Protocols	Main Results
Holditch-Davis et al. (2001)[47]	United States	81 HEU = 81	BSID-II	The quality of parenting and the consistency of the primary caregiver influence the developmental outcomes of HEU children.
Bruck et al. (2001)[39]	Brazil	150 HEI = 43 HEU = 40 HUU = 67	DDST and CAT/CLAMS	Hyperactivity, irritability, and hypotonia were the findings on neurological examination, with no statistical differences between the HEI and HEU groups. In the CAT/CLAMS, the developmental quotient of the HEI group was significantly lower than that of the other groups. The same occurred in the DDST, with the HEI group showing significantly more abnormalities than the HEU group.
Gontijo et al. (2001)[36]	Brazil	28 HEI = 11 HEU = 3 HUU = 14	DDST and BSID	HEI children exhibit NPMD delay compared to HUU children of the same age, socioeconomic level, and demographic conditions.
Blanchette et al. (2001)[40]	Canada	50 HEI = 25 HEU = 25	BSID	Infants in the HEI group had significantly lower motor and cognitive scores compared to infants in the HEU group, and abnormalities on CT scan were associated with these delays.
Llorente et al. (2003)[51]	United States and Puerto Rico	157 HEI = 157	BSID	It suggests that low cognitive and psychomotor scores at 4 months are significant predictors of early mortality in HEI children.
Alimenti et al. (2006)[41]	Canada	63 HEU = 39 HUU = 24	BSID-II	Exposure of HEU children to highly active antiretroviral therapy (HAART) is not associated with changes in developmental measures."
Lindsey et al. (2007)[50]	United States	1204 Pré-TARV HEI = 54 HEU = 221 Pós-TARV HEI = 91 HEU = 838	BSID	In the pre-ART era, the mean cognitive and motor scores in HEI children under one year of age were significantly lower than those of HEU children and remained lower up to two years of age. After ART became available, cognitive and motor functioning in HEI children under one year of age remained significantly lower than that of HEU children. However, in a context of declining scores among HEU children, there was evidence of only limited improvement among HEI children compared to their uninfected peers. Among children who underwent Bayley II assessments before and after starting ART, there was a trend toward improved mental and motor scores following initiation of antiretroviral therapy.
Baillieu et al. (2008)[12]	South Africa	40 HEI = 40	BSID-II	Eighty-five percent showed motor developmental delay and 82.5% showed language delay. In HEI children, cognitive delay may occur due to disease progression and structural brain damage, while language delay may be attributed to neurological impairment, cognitive delay, or environmental deprivation.
Gómez et al. (2009)[43]	Colombia	43 HEU = 23 HUU = 20	DDST-II and BSID-II	Intrauterine exposure to HIV and antiretrovirals in HEU infants does not cause changes in NPMD.
Van Rie et al. (2009)[65]	South Africa	160 HEI = 35 HEU = 35 HUU = 90	BSID-II	At baseline, HEI children had the lowest average developmental scores, HUU children had the highest, and HEU children had intermediate average scores. After 1 year of treatment, HEI children achieved average motor and cognitive scores similar to HEU children, although lower compared to HUU children.
Hokjindee et al. (2010)[66]	Thailand	143 HEU = 53 HEI = 2 SS = 88	DDST-II	The risk of developmental delay was present in 15.4% of the total sample, with nutritional deficiency being more common than delays in NPMD among children born to HIV+ mothers.
Potterton et al. (2010)[13]	South Africa	122 HEI in HSP = 60 HEI without HSP = 62	BSID-II	Cognitive and motor development were severely affected at the beginning of the study, with 52% of the children exhibiting severe cognitive delay and 72% exhibiting severe motor delay. Children in the Home Stimulation Programme (HSP) showed significantly greater improvement in cognitive and motor development over time compared to children in the other group.
Ramos et al. (2011)[38]	Brazil	12 HEU = 12	DDST-II	About 50% of the children evaluated were at risk of delayed NPMD, which may be related not only to biological factors, such as exposure to HIV and ART during pregnancy, but also to the presence of adverse environmental factors that compromise NPMD.
Kandawasvika et al. (2011)[80]	Zimbabwe	598 HEI = 65 HEU = 188 HUU = 287 SS = 58	BINS	The high risk of delay in NPMD was twice as high in the HEI group compared to uninfected infants.
Lowick et al. (2012)[24]	South Africa	60 HEI = 30 HUU = 30	GMDS-ER	There was a 7.88 times higher probability of severe delay in the HIV-infected group. Early initiation of ART in HIV-infected infants may improve cognitive function in this group; however, intervention strategies that optimise early cognitive development for all children in the area need to be urgently considered.
Sirois et al. (2013)[53]	United States and Puerto Rico	423 HEU = 374 HUU = 49	BSITD-III	The results demonstrate the safety of using ART during pregnancy and the prenatal period. The mean Bayley-III scores for HIV-exposed and unexposed infants were similar and within age expectations.
McDonald et al. (2013)[69]	Tanzania	311 HEI = 31 HEU = 280	BSID-II	Infant HIV status, gestational age at birth, stunting, and weight loss were significant and independent correlates of cognitive and psychomotor development among infants born to HIV-infected women.
Manji et al. (2014)[68]	Tanzania	206 HEU = 206	BSITD-III	Daily multivitamin supplementation for HIV-exposed infants does not substantially improve NPMD outcomes at 15 months.
Whitehead et al. (2014)[25]	South Africa	55 HEU = 29 HEI = 26	BSITD-III	This study suggests that HIV-positive infants are delayed when compared to HEU infants. HAART may help to prevent further delay; however, it does not reverse the neurological damage already present.
Brahmbhatt et al. (2014)[71]	Uganda	329 HEI = 116 HEU = 105 HUU = 108	MSEL and ELC	HEI children were more likely to have developmental deficits in NPMD, and prolonged ART use potentially mitigated some of the neurodevelopmental deficits.
Ngoma et al. (2014)[79]	Zambia	200 HEU = 97 HUU = 103	FSDQ and CAT/CLAMS	The study did not find any differences in NPMD between the groups, nor did it observe any adverse effects in HEU children exposed to ART in utero and during one year of breastfeeding.
Dara et al. (2015)[60]	Malawi	33 HEI =33	BSITD-III	The hypothesis of milder neuropathology in individuals infected with the HIV Tat^CS variant was not confirmed in the HEI cohort.
Benki-Nugent et al. (2015)[64]	Kenia	99 HEI = 99	DDST	HIV disease progression, poor growth, and inadequate response to ART were associated with an older age at achieving developmental milestones in HEI infants.
Bass et al. (2016)[72]	Uganda	339 HEI = 118 HEU = 221	MSEL	No difference was observed in NPMD between HEI and HEU children. The results indicate that the child's initial home environment is associated with general cognitive development. Complex environments in the context of poverty and HIV can impact cognition and neurodevelopment.
Boivin et al. (2017)[73]	Uganda	221 HEU = 221	MSEL	Although the Mediational Intervention for Sensitizing Caregivers (MISC) programme demonstrated an improvement in the quality of caregiving, it did not yield better cognitive outcomes in children compared with training in health and nutrition.
Chaudhury et. al. (2017)[32]	Botswana	670 HEU = 313 HUU = 357	BSITD-III and DMC	HEU children performed equally well on neurodevelopmental assessments at 24 months compared to the HUU group.
Silva et al. (2017)[37]	Brazil	80 HEU = 40 HUU = 40	BSITD-III	Infants exposed to HIV and antiretroviral therapy exhibited appropriate cognitive and motor development during the first 18 months. However, the lower scores found, particularly at the 8th and 18th months for cognitive development, may indicate future problems, highlighting the need for systematic monitoring of this population.
Smith et al. (2017)[42]	Canada	64 HEU = 64	Wechsler-III and Vineland-2 and VMI	The results suggest that children exposed to HIV and antiretroviral therapy in utero and early life may experience late NPMD changes.

Author (year)	Place	Sample	Protocols	Main Results
Rajan et al. (2017)[57]	India	50 HEU = 41 HEI = 9	DASII	The development of HEU children was negatively affected by lower socioeconomic status and the presence of weight loss. Furthermore, the development of HEI children was negatively influenced by the presence of stunting, opportunistic infections, advanced disease stage, and shorter ART duration. We conclude that, with optimal care, the HEU group can achieve normal development, whereas a significant proportion of HEI children may continue to experience delayed development.
Shariat et al. (2017)[59]	Iran	75 HEI = 28 HUU = 47	WHO Milestone Chart and ASQ	Some NPMD disorders in HEI children were more frequent than in HUU children but can be stabilized with the use of ART and family guidance.
Benki-Nugent et al. (2017)[63]	Kenia	155 HEI = 63 HUU = 92	DDST	HIV-infected infants with viral suppression on ART had better recovery of developmental milestones than those without suppression; however, deficits persisted compared to uninfected infants.
Dalili et al. (2018)[87]	Iran	39 HEU = 39	WHO Milestone Chart e ASQ	The prevalence of NPMD disorders, including delays in language, motor, and social domains, was common among HEU children. As various environmental factors may be involved in the etiology of neurodevelopmental disorders, postnatal control and prevention are necessary.
Laughton et al. (2018)[26]	South Africa	109 HEI = 36 HEU = 34 HUU = 39	GMDS	Five-year neurodevelopmental outcomes in HIV-infected children who received early, time-limited ART were similar to those of uninfected controls, except in visual perception, where their scores were lower.
Rodriguez et al. (2018a)[28]	South Africa	69 HEU = 69	BSITD-III	This study highlights that not living with the male partner, not disclosing one's HIV status, and experiencing postpartum depression predicted cognitive delay; and diminished prenatal male involvement predicted motor development delay.
Rodriguez et al. (2018)	South Africa	72 HEU = 67 HEI = 5	BSITD-III	Early exposure to postnatal intimate partner violence was associated with cognitive delay and receptive communication delay in infants.
Le Roux et al. (2018)[29]	South Africa	521 HEU = 215 HUU = 306	BSITD-III	Young HEU children may be at increased risk of cognitive and motor delay, despite universal maternal ART and breastfeeding. Preterm infants may be more vulnerable.
Springer et al. (2018)[30]	South Africa	96 HEU = 58 HUU = 38	BSITD-III	There was no difference in NPMD at 12 months between HEU and HUU children. However, slight differences in neurological assessments and vocalization patterns indicate the need for follow-up evaluation at a later age.
Chaudhury et al. (2018)[33]	Botswana	598 HEU = 598	BSITD-III DMC	The neurodevelopment of HEU children at 24 months does not differ based on in-utero exposure to ART. Maternal ART combined with breastfeeding does not appear to have an adverse effect on neurodevelopment.
Kacanek et al. (2018)[34]	Botswana	197 HEU = 197	BSITD-III	Neurodevelopmental outcomes at 24 months for HEU children born to mothers with CD4 ≥ 200 were similar between HEU children randomized to receive dual-NRTI–based ART and those randomized to receive triple-NRTI–based ART. This study showed that ART has low toxicity in the short-term follow-up.
Wu et al. (2018) [44]	China	500 HEU = 250 HUU = 250	BSITD-III	HIV-exposed but uninfected children had significantly lower Bayley-III scores than HUU children.
Gómez et al. (2018)[62]	Kenia	74 HEI= 74	MDAT	It evaluated the influence of ART initiated within the first 48 hours after birth on neurodevelopment at six months of age. The children made significant gains in neurological development during six months of ART. Children who experienced better growth and immune recovery showed greater improvement. Immediate initiation of ART may improve neurodevelopment, in addition to supporting immune recovery and growth.
Ruiseñor-Escudero et al. (2018)[7]	Uganda	308 HEI = 87 HEU = 221	MSEL and COAT and ECVT	Neurodevelopmental scores among children aged 2 to 5 years infected with HIV were similar for subtypes A and D, with few potential differences in language production and memory outcomes that favored subtype A.
Familiar et al. (2018)[75]	Uganda	215 HEU = 75 HUU = 140	MSEL	HIV exposure is associated with lower scores in infant cognitive development.
Mebrahtu et al. (2018)[83]	Zimbabwe	397 HEU = 381 HEI = 16	MSEL	The results show an association between maternal mood and stress levels and cognitive functioning in HEU children, specifically in expressive language and visual reception domains.
Cassidy et al. (2019)[35]	Botswana	493 HEU = 493	BSITD-III	HEU children exposed in utero to efavirenz-based ART may have a higher risk of neurodevelopmental and socio-emotional deficits compared to children exposed to conventional ART.
Alcaide et al. (2019)[31]	South Africa	80 HEU = 80	BSITD-III	The results showed a risk of cognitive developmental delay associated with the use of ART during pregnancy and intimate partner violence.
Le Roux et al. (2019)[14]	South Africa	214 HEU = 214	BSITD-III	Maternal cumulative HIV viremia during pregnancy may have adverse effects on neurodevelopment in HEU children.
Wedderburn et al. (2019)[15]	South Africa	At 6 months (n = 260) HEU = 61 HUU = 199 At 24 months (n = 732) HEU = 168 HUU = 564	BSITD-III	HEU children exposed in utero to maternal ART may have a higher risk of delays in receptive and expressive language development at 24 months compared to HUU children.
Pamplona et al. (2019)[84]	Brazil	118 HEU = 60 HUU = 58	DDST-II	Maternal HIV-1 infection negatively affected neuropsychomotor development in children, although other factors may have influenced this outcome. A child diagnosed with HIV had the worst outcomes.
Jantarabenjakul et al. (2019)[85]	Thailand	150 HEI = 50 (HEI = 27 children with immediate ART upon diagnosis and HEI = 23 late ART) HEU = 100	MSEL	Preschool-aged HEU children who initiated ART within the first 3 months of life exhibited a global developmental delay rate comparable to that of HUU children.
Cox et al. (2020)[16]	South Africa	60 HEU =30 HUU = 30	BSITD-III	In utero exposure to HIV and ART appears to have minimal impact on child development.
Cornelia de Beer et al. (2020)[17]	South Africa	81 HEU = 41 HUU = 40	Vineland-3	The developmental outcomes of HEU children during early childhood are not significantly different from those of the HUU group.
Gruver et al. (2020)[18]	South Africa	922 HEU = 257 HUU = 627 HEI = 38	K-ABC	The HEU group does not differ from the HUU group in their cognitive and language profiles between 4 and 6 years of age, but HEI children had significantly lower scores.
Springer et al. (2020)[19]	South Africa	59 HEU = 32 HUU = 27	BSID	HIV exposure did not confer additional risk to neurodevelopment. Growth delay was associated with increased behavioral problems, regardless of HIV exposure

Author (year)	Place	Sample	Protocols	Main Results
Strehlau et al. (2020)[20]	South Africa	49 HEU = 49	BSITD-III	No developmental delay was found at 12 months of age among HEU children exposed to maternal ART.
White et al. (2020)[21]	South Africa	54 HUU = 22 HEU = 32	GMCD	The main findings showed that there was no significant difference between HUU and HEU infants in the proportion who achieved neurodevelopmental milestones at 1–3 months of age. By 3–5 months of age, most infants achieved the expected developmental milestones. However, HUU infants exhibited difficulties with receptive language milestones, gross motor development, and play behavior during 1–3 months of age, whereas HEU infants faced challenges in fine motor milestones between 3–5 months.
Jao et al. (2020)[52]	United States and Puerto Rico	678 HEU = 678	BSITD-III	HEU children born to mothers with perinatally acquired HIV did not show an increased overall risk of cognitive developmental deficits during the first year of life, compared to HEU children born to mothers who did not acquire HIV perinatally. The differences (modest but significant) occurred in language and motor development.
Mebrahtu et al. (2020)[78]	Zimbabwe	514 WS = 514	MSEL	There is a strong association between NPMD alterations and children whose mothers have conditions such as depression and anxiety.
Ntozini et al. (2020)[77]	Zimbabwe	1380 HEU = 205 HUU = 1175	MDAT	Language and motor skills at two years of age were lower among HEU children compared to HUU children.
Sevenoaks et al. (2021)[22]	South Africa	267 HEU = 77 HUU = 190	BSITD-III	Maternal HIV infection is associated with immune dysregulation, with results indicating suppressed serum inflammatory markers in HIV-positive mothers and HEU children up to two years of age. Results also show that an altered immune system in HEU infants is associated with poorer motor development in children at two years.
Matseke et al. (2021)[23]	South Africa	160 WS = 160	BSITD-III	High levels of delay were detected in cognitive, communicative, fine motor, and gross motor development in children born to HIV-positive mothers.
Mchenry et al. (2021)[61]	Kenia	172 HEI = 24 HEU = 74 HUU = 74	BSITD-III	No statistically significant differences were found among the three groups (HEI, HEU, and HUU) in the assessed skills (cognition, expressive language, fine and gross motor), with the exception that children who were HIV+ were found to have higher receptive language scores than others.
Sirajee (2021)[11]	Uganda	170 HEU = 170	MDAT	Delayed growth in HEU children was associated with poorer attainment of developmental milestones at 18 months.

Abbreviations: HEI = HIV-positive children born to HIV-positive mothers during pregnancy // HEU = HIV-negative children born to HIV-positive mothers during pregnancy // HUU = HIV-negative children born to HIV-negative mothers during pregnancy // WS = children without serology, born to HIV-positive mothers // BSID = Bayley Scales of Infant Development // BSID-II = Bayley Scales of Infant Development, Second Edition // BSITD-III = Bayley Scales of Infant and Toddler Development, third edition // BINS = Bayley Infant Neurodevelopmental Screener // ECSP = Early Childhood Screening Profiles // DDST = Denver Developmental Screening Test // DDST- II = Denver II Development Screening Test //CAT/CLAMS = Clinical Linguistic and Auditory Milestone Scale // MSEL = Mullen Scales of Early Learning // ECSP = Early Childhood Screening Profiles // PLS-3 = Preschool Language Scale, Version 3 // VABS = Vineland Adaptive Behavior Scale // CAT/CLAMS = Capute Scales Clinical Adaptive Test/Clinical Linguistic and Auditory Milestone Scale // GMDS-ER = Griffiths Mental Development Scales-Extended Revised Version // ELC = Early Learning Composite // FSDQ = Capute Full-Scale Developmental Quotient // DMC = Development Milestones Checklist // DASII = Development Assessment scale for Indian Infants // Vineland-3 = Vineland Adaptive Behavior Scales, Third Edition // Wechsler-III = Wechsler Preschool and Primary Scale of Intelligence 3rd edition // Vineland-2 = Vineland Adaptive Behavior Scales 2nd edition // VMI = Developmental Test of Visuomotor Integration // WHO = World Health Organization Milestones Chart // ASQ = Age and Stage Questionnaire // GMCD = Guide for Monitoring Child Development // MDAT = Malawi Developmental Assessment Tool // COAT = Color Object Association Test // ECVT = Early Childhood Vigilance Test // K-ABC = Kaufman Assessment Battery for Children // GMDS = Griffiths Mental Development Scales // K-ABC = Kaufman Assessment Battery for Children // FSDQ = Capute Full-Scale Developmental Quotient // DASII = Development Assessment scale for Indian Infants // DMC = Development Milestones Checklist.

It was observed that the studies presented various configurations of study groups with the aim of analyzing neuropsychomotor development. A total of 18,043 children were evaluated, divided into groups according to the serological status of the child and the mother, as follows: HEI – HIV-positive children born to HIV-positive mothers during pregnancy (n = 2,119); HEU – HIV-negative children born to HIV-positive mothers during pregnancy (n = 9,624); HUU (control group) – HIV-negative children born to HIV-negative mothers (n = 5,481); and WS – children without HIV serology, born to HIV positive mothers (n = 820). The largest group consisted of HIV negative children born to HIV positive mothers.

The studies that compared HEI, HEU, and HUU numbered 12. Those that evaluated only HEI numbered seven; those that evaluated only HEU numbered 15; those that compared HEI with HEU numbered 12; those comparing HEI with HUU numbered six; and those comparing HEU with HUU numbered 18. And the studies that compared all three groups (HEI, HEU, and HUU) numbered 12, including one study with only WS, one comparing HEU, HEI, HUU and WS, and one study comparing HEU, HEI and WS.

To assess neuropsychomotor development, the majority of studies (60.3%, n = 44) used the Bayley Scales of Infant Development in various editions, followed by the Denver Developmental Screening Test (12.3%, n = 9) and the Mullen Scales of Early Learning (10.9%, n = 8). However, a variety of other protocols were also used, namely: Early Childhood Screening Profiles (ECSP); Preschool Language Scale, Version 3 (PLS 3); Vineland Adaptive Behavior Scale (VABS); Capute Scales Clinical Adaptive Test/Clinical Linguistic and Auditory Milestone Scale (CAT/CLAMS); Griffiths Mental Development Scales-Extended Revised Version (GMDS-ER); Early Learning Composite (ELC); Capute Full-Scale Developmental Quotient (FSDQ); Development Milestones Checklist (DMC); Development Assessment Scale for Indian Infants (DASII); Vineland Adaptive Behavior Scales, Third Edition (Vineland-3); Wechsler Preschool and Primary Scale of Intelligence 3rd edition (Wechsler-III); Vineland Adaptive Behavior Scales 2nd edition (Vineland-2); Developmental Test of Visuomotor

Integration (VMI); World Health Organization (WHO) Milestones Chart; Age and Stage Questionnaire (ASQ); Guide for Monitoring Child Development (GMCD); Malawi Developmental Assessment Tool (MDAT); Color Object Association Test (COAT); Early Childhood Vigilance Test (ECVT); Kaufman Assessment Battery for Children (K-ABC); Griffiths Mental Development Scales (GMDS).

Of the 73 studies included in this scoping review, 51 (69.9%) assessed children infected with HIV who were born to HIV-positive mothers, and in all of these studies, the children exhibited significant delays in NPMD, in comparison to both HEU and HUU children. When the studies assessing NPMD of HIV-negative children born to HIV-positive mothers were analyzed, the findings were controversial. Some studies observed NPMD alterations in HEU children when compared to HUU children, while others did not observe differences between the development of HEU and HUU children.

In the methodological quality assessment, the risk of bias was considered low in 69.9% of studies and moderate in 30.1%. (Table 2).

Table 2. Methodological quality assessment of the studies.

AUTHOR(YEAR)	TYPE	MQA	
Baillieu et al. (2008)	CACSS	5.75	Moderate
Van Rie et al. (2008)	CACSS	6.5	Low
Potterton et al. (2010)	CSS	8.5	Low
Hilburn et al. (2011)	CACSS	4.5	Moderate
Lowick et al. (2012)	CACSS	8.75	Low
Whitehead et al. (2014)	CCS	8.75	Low
Boyede et al. (2016)	CACSS	6.5	Low
Strehlau et al. (2016)	CCS	6.75	Moderate
Knox et al. (2018)	CCS	7	Moderate
Laughton et al. (2018)	CCS	10.25	Low
Rodriguez et al. (2018)	CACSS	7.5	Low
Rodriguez et al. (2018)	CACSS	8	Low
Roux et al. (2018)	CCS	9	Low
Springer et al. (2018)	CCS	8	Low
Alcaide et al. (2019)	CACSS	7.25	Low
Roux et al. (2019)	CCS	8.25	Low
Wedderburn et al. (2019)	CCS	9.5	Low
Cox et al. (2020)	CACSS	5.5	Moderate
Beer et al. (2020)	CACSS	6.5	Low
Gruver et al. (2020)	CACSS	8	Low
Rodriguez et al. (2020)	CACSS	7	Low
Springer et al. (2020)	CCS	9.25	Low
Streahlau et al. (2020)	CCS	8	Low
White et al. (2020)	CCS	8.75	Low
Sevenoaks et al. (2021)	CCS	10	Low
Matseke et al. (2021)	CCS	7.5	Moderate
Chaudhury et al. (2017)	CCS	10.25	Low
Chaudhury et al. (2018)	CCS	8	Low
Kacanek et al. (2018)	CCS	9	Low
Cassidy et al. (2019)	CCS	7	Moderate
Bruck et al. (2001)	CCS	7	Moderate
Gontijo et al. (2001)	CACSS	6	Moderate
Ramos et al. (2011)	CACSS	5	Moderate
Silva et al. (2017)	CACSS	6.5	Low
Pamplona et al. (2019)	CCS	8	Low
BlanHEUtte et al. (2001)	CACSS	5.25	Moderate
Alimenti et al. (2006)	CACSS	7.5	Low
Smith et al. (2017)	CCS	8.75	Low
Gómez et al. (2009)	CCS	8.5	Low
Wu et al. (2018)	CCS	7.75	Low
Aylward et al. (1992)	CCS	10	Low
Chase et al. (1995)	CCS	10	Low
Pollack et al. (1996)	CCS	8	Low
Knight et al. (2000)	CCS	9.5	Low
Holditch-Davis et al. (2001)	CCS	10.5	Low
Lindsey et al. (2007)	CCS	7	Moderate
Williams et al. (2010)	CCS	7	Moderate
Chase et al. (2000)	CCS	10.5	Low
Smith et al. (2000)	CCS	8	Low
Llorente et al. (2003)	CCS	10	Low
Sirois et al. (2013)	CCS	7.5	Moderate
Jao et al. (2020)	CCS	7.5	Moderate
Gay et al. (1995)	CCS	9	Low
Rajan et al. (2017)	CCS	8.25	Low
Shariat et al. (2017)	CCS	6.75	Moderate
Dalili et al. (2018)	CCS	7.25	Moderate
Dara et al. (2015)	CCS	10.5	Low
Nugent et al. (2015)	CCS	8	Low
Nugent et al. (2017)	CCS	10.25	Low
Gómez et al. (2018)	CCS	9	Low
Mchenry et al. (2021)	CACSS	6.25	Moderate
Van Rie et al. (2009)	CCS	7.25	Moderate
Msellati et al. (1993)	CCS	7.25	Moderate
Hokjindee et al. (2010)	CCS	8.25	Low
Jantarabenjakul et al. (2019)	CCS	8.75	Low
McGrath et al. (2006)	CCS	8	Low
McDonald et al. (2013)	CCS	8	Low
Manji et al. (2014)	CCS	9	Low
Drotar et al. (1999	CCS	9	Low
Brahmbhatt et al. (2014)	CCS	8.25	Low
Bass et al. (2016)	CCS	7.5	Moderate
Boivin et al. (2017)	CCS	8	Low

Abbreviations: MQA = Methodological quality assessment // Type = type of protocol used // CCS = checklist for cohort studies // CACSS = checklist for analytical cross-sectional studies.

This study aimed to understand how HIV influences neuropsychomotor development in both children who were exposed to the virus in utero and became infected, as well as in children who were only exposed in utero but did not become infected. For this purpose, the articles selected in this review present studies that evaluate the neuropsychomotor development of children who were exposed but uninfected (HEU), exposed and infected (HEI), and children who are neither exposed nor infected (HUU).

Among the groups addressed in this research, the most vulnerable to alterations in neuropsychomotor development (DNPM) was the group of children who were exposed to and infected with HIV and who were not using antiretroviral therapy. Several studies have demonstrated deficits in neurodevelopment in the HEI children. The studies that associated child development with the use of ART observed that the earlier the infant begins ART, the fewer the impairments in neuropsychomotor development (especially when the viral load becomes undetectable), and that even in cases of later initiation, ART is beneficial and helps prevent further delays, although it does not reverse neurological damage already present.[25,49,63]

Additionally, the studies show that developmental alterations can be identified as early as in the first months of life and are directly related to Aids

progression, such that they are even used as one of the parameters for monitoring disease evolution and severity and for classifying HIV infection according to the Centers for Disease Control and Prevention (CDC).[55,67]

Delay in neuropsychomotor development can occur due to disease progression and brain structural damage resulting from the direct action of the virus in the central nervous system, as well as exposure to environmental risk factors.[12] Studies have confirmed neurological deficits and the virus's damaging action in the CNS in infected children, linked to developmental alterations, demonstrating the neurotropism of the virus.[81,82]

To understand neuropsychomotor development and the mechanisms that can alter its progression, it is necessary to also analyze the factors that may influence this process beyond HIV itself. The researchers highlighted the effects of the home environment in which the child is raised within a context of poverty and HIV, socioeconomic status, maternal schooling, the child's nutritional status, maternal mood and stress levels in HIV-positive mothers, maternal depression, parental separation, maternal death, and low income on the overall cognitive development of infected infants.[56,72,83,84]

The authors emphasized the importance of strategies to reduce vertical transmission, promote child growth, prevent preterm birth, and ensure follow up monitoring of the development of these children.[36,48,69] The main way to reduce or even eliminate the influence of HIV on neuropsychomotor development in infected children nowadays is antiretroviral therapy (ART). According to the literature, when evaluating and comparing children exposed and infected with HIV who started ART early, with groups of uninfected HIV-exposed children and unexposed children over an extended period, it was shown that HEI had similar outcomes compared to HUU, even demonstrating restoration of neurodevelopment and viral suppression, thereby highlighting the importance of early intervention with ART. Other factors have been cited in this regard, such as the importance of nutritional and social support, as well as improvements in motor and cognitive development associated with early intervention.[23,63,85,65]

Several studies suggest that prenatal and postnatal exposure (up to the first 25 months of life in children exposed to HIV) to antiretroviral therapy is not associated with alterations in neuropsychomotor developmental skills.[20,26,29,34,41,42,79,86] A study conducted in Kenya that used delayed antiretroviral therapy intervention for a period of six months achieved significant gains in gross and fine motor functioning, growth, and immune system performance.[62] However, language and social functioning did not improve overall; even with the gains observed, the scores still remained below African norms, which corroborates findings from other studies. These studies help us understand how early intervention makes a difference, but also what benefits delayed intervention can bring.[50,71]

Although infants' exposure to an excess of medications brings benefits, it still requires caution due to their potential toxicity. The study conducted in Botswana enrolled a total of 493 children at 24 months of age to evaluate the neuropsychomotor development of HEU infants who had in utero exposure to Efavirenz (EFV)-based triple antiretroviral therapy. This study found an association between EFV exposure and reduced scores in receptive language as well as gross and fine motor skills.[35] A study evaluating children at around 24 months also found alterations in receptive and expressive language abilities among HEU children. When language skills are impaired, they are a strong risk factor for children exposed to HIV, as they lead to future learning disadvantages.[82,73]

The results of a Canadian study suggest that children with early exposure to ART may have inferior neurocognitive performance compared with their peers at the end of preschool.[24] The authors state that, despite ART and breastfeeding, children may have an increased risk of delay in cognitive and motor development. However, researchers cite that the use of ART during pregnancy, combined with breastfeeding, outweighs the possible risks for children exposed to HIV. However, the importance of programs for prevention of vertical transmission is emphasized. A study carried out in Zimbabwe with 540 children evaluated a vertical transmission prevention program, and the results showed a prevalence of 9.4% among the high risk HEI and HEU groups for neurodevelopmental impairment.[33,42,80]

Other studies have shown that antiretroviral therapy reduces the effects of HIV; however, when compared with HIV exposed children, a delay in neurodevelopment was observed.[42,45] A study that evaluated the neurodevelopment of children before the initiation of ART and after viral suppression promoted by the treatment identified a significant improvement in this aspect. However, a high prevalence of neurodevelopmental delays was observed, highlighting the need for additional interventions to enhance the outcomes achieved with ART. One example of an intervention that can help is the prevention program for mother-to-child transmission implemented in a 2010 study; this program encompassed everything from maternal antiretroviral therapy to free prenatal guidance courses for expectant mothers. Of the 143 children evaluated who participated in this program, only 2 (1.3%) tested positive for HIV. Another example is the home-based intervention program focused on caregiving, discussed by authors, which can bring

significant improvements to cognitive and motor development.[21,30,66]

When comparing the HEI and HEU groups, researchers reported that during the first two years, developmental delays occurred more frequently in infected children than in exposed children; these children even showed outcomes similar to those of uninfected and unexposed children.[57,67]

Unlike the group of HIV-exposed and infected children, where neurodevelopmental impairment is more prevalent, studies observe that HIV-exposed but uninfected children may exhibit more subtle changes or no neuropsychomotor development alterations. Some studies comparing HEU with HUU children assessed neurodevelopmental skills in children aged 12 months to 6 years, some of whom were socioeconomically matched and others were not, and no significant differences were found between the groups.[25,27,28,31,87]

However, other researchers focusing on children aged one month to two years exposed to HIV found significant differences demonstrating that HIV exposure can impair neuropsychomotor development skills, with alterations in the immune system associated with this impairment, highlighting the importance of early interventions for these children.[15,16,77]

An important issue for the group of HIV-exposed uninfected children is the biopsychosocial factors. Researchers have demonstrated that factors such as the presence of the father, antiretroviral use, intimate partner violence during and after pregnancy, parenting quality, maternal characteristics, caregiver consistency, maternal care quality, and common mental disorders (depression, anxiety, and somatic symptoms), when associated with HIV exposure in these children, can influence the skills that are part of the neuropsychomotor development.[17,47,75,78]

Despite the extensive literature on the subject and the quality of existing studies, researchers still cannot elucidate the true influence of HIV exposure and ART during pregnancy, as well as environmental factors, on the neurodevelopmental progress of HIV exposed, uninfected children; thus, new studies with greater control over the variables are needed. Given that the contributing factors remain unclear, it is important to highlight the need for long term monitoring of these babies who were exposed to HIV during in utero development, especially when we consider how rapidly ART use is expanding and the increasing variety of drugs being developed.

CONCLUSION

The studies analyzed showed that HIV exposure during pregnancy is not determinative of alterations in the neuropsychomotor development, instead, it is the HIV infection itself, given the action of the virus on the central nervous system. However, HIV-exposed children in utero, but uninfected, may also experience alterations in the neuropsychomotor development mainly associated with environmental factors, highlighting the importance of longitudinal monitoring of all children born to HIV-positive mothers, regardless of infection status.

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AUTHORS' CONTRIBUTIONS

Raphaela Barroso Guedes-Granzotti contributed to the conception, article design, critical analysis, and final draft of the article. **Matheus do Nascimentos Alves** contributed to the literature search, data collection, and writing of the article. **Lara Suzana de Oliveira Nunes** contributed to the literature search, data collection, and writing of the article. **Nathália Monteiro Santos** contributed to the literature search, data collection, and writing of the article. **Vinicius Nunes Araujo** contributed to the literature search, data collection, and writing of the article. **Carla Patrícia Hernandez Alves Ribeiro César** contributed to the conception, article design, critical analysis, and final draft of the article. **Kelly da Silva** contributed to the conception, article design, critical analysis, and final draft 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

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Case Report

Importance of Differential Diagnosis in Patients with Community-Acquired Pneumonia Using K-9 Drugs (spice)

Importância do diagnóstico diferencial em pacientes com Pneumonia Adquirida na Comunidade, em uso de drogas K-9 (spice)
Importancia del diagnóstico diferencial en pacientes con Neumonía Adquirida en la Comunidad que consumen drogas K-9 (spice)

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Corresponding author:
E-mail: azttalk@gmail.com
Address: Abraão Caixe Street, 380, Ribeirão Preto, São Paulo, Brazil.

André Zitelli[1]
Álvaro Henrique Volpini Vilera[1]
Larissa Pereira da Silva[1]
Luis Gustavo Durante Bacelar[1]
Luiz Paulo Furtado Pompolim[1]
Victor de Albuquerque Orsolin[1]
Silvia Nunes Szente Fonseca[1]

[1]University Center Estácio Idomed, Ribeirão Preto, São Paulo, Brazil.

ABSTRACT

Community-acquired pneumonia (CAP) is a condition with high morbidity and mortality, particularly among users of inhaled drugs. The use of the synthetic drug K9 (spice) has been associated with chemical pneumonitis, whose clinical presentation can mimic respiratory infections, complicating diagnosis and appropriate management. This study reports the case of a 33-year-old male patient with a history of substance dependence and recent K9 use, who was hospitalized with severe respiratory failure. Laboratory tests, chest computed tomography, and microbiological and molecular analyses for infectious agents were performed. Initial treatment included empirical antibiotic therapy, invasive ventilatory support, and systemic corticosteroids. The absence of identifiable pathogens and compatible radiological findings led to the diagnosis of K9-induced chemical pneumonitis. Corticosteroid therapy resulted in progressive clinical improvement, allowing extubation and hospital discharge after 24 days, with referral for rehabilitation. This case highlights the importance of considering synthetic drugs in the differential diagnosis of CAP in young individuals with a history of substance use, preventing unnecessary antibiotic use and ensuring more targeted treatment. Additionally, it underscores the need for professional training to recognize clinical and radiological patterns suggestive of chemical pneumonitis, as well as the development of public policies aimed at preventing synthetic drug use and mitigating its impact on public health.

Keywords: *Pneumonia. Pneumonitis. Illicit drugs. Substance abuse.*

RESUMO

A Pneumonia Adquirida na Comunidade (PAC) é uma condição de alta morbimortalidade, especialmente em usuários de drogas inalatórias. O uso da droga sintética K9 (*spice*) tem sido associado à pneumonite química, cujo quadro clínico pode ser confundido com infecções respiratórias, dificultando o diagnóstico e o manejo adequado. Este estudo relata o caso de um paciente masculino, 33 anos, com dependência química e uso recente de K9, internado com insuficiência respiratória grave. Foram realizados exames laboratoriais, tomografia computadorizada de tórax e pesquisa de agentes infecciosos por culturas microbiológicas e testes moleculares. O tratamento inicial incluiu antibioticoterapia empírica, suporte ventilatório invasivo e corticosteroides sistêmicos. A ausência de patógenos identificáveis e os achados radiológicos compatíveis levaram ao diagnóstico de pneumonite química induzida por K9. A terapia com corticosteroides promoveu melhora progressiva, permitindo a extubação e alta hospitalar após 24 dias, com encaminhamento para reabilitação. O caso destaca a importância de considerar drogas sintéticas no diagnóstico diferencial da PAC em indivíduos jovens com histórico de uso de substâncias, evitando o uso desnecessário de antibióticos e garantindo um tratamento mais direcionado. Além disso, evidencia a necessidade de capacitação profissional para o reconhecimento de padrões clínicos e radiológicos sugestivos de pneumonite química, bem como o desenvolvimento de políticas públicas voltadas à prevenção do consumo de drogas sintéticas e à mitigação de seus impactos na saúde pública.

Descritores: *Pneumonia. Pneumonite. Drogas ilícitas. Dependentes químicos.*

RESUMEN

La Neumonía Adquirida en la Comunidad (NAC) es una condición con alta morbilidad y mortalidad, especialmente en usuarios de drogas inhalatorias. El consumo de la droga sintética K9 (spice) se ha asociado con neumonitis química, cuya presentación clínica puede confundirse con infecciones respiratorias, dificultando el diagnóstico y el manejo adecuados. Este estudio reporta el caso de un paciente masculino de 33 años, con antecedentes de dependencia a sustancias y consumo reciente de K9, hospitalizado con insuficiencia respiratoria grave. Se realizaron análisis de laboratorio, tomografía computarizada de tórax y estudios microbiológicos y moleculares para detección de agentes infecciosos. El tratamiento inicial incluyó antibioticoterapia empírica, soporte ventilatorio invasivo y corticosteroides sistémicos. La ausencia de patógenos identificables y los hallazgos radiológicos compatibles llevaron al diagnóstico de neumonitis química inducida por K9. La terapia con corticosteroides resultó en una mejoría clínica progresiva, permitiendo la extubación y el alta hospitalaria tras 24 días, con derivación a rehabilitación. Este caso destaca la importancia de considerar las drogas sintéticas en el diagnóstico diferencial de la NAC en individuos jóvenes con antecedentes de consumo de sustancias, evitando el uso innecesario de antibióticos y asegurando un tratamiento más adecuado. Además, evidencia la necesidad de capacitar a los profesionales de la salud para reconocer patrones clínicos y radiológicos sugestivos de neumonitis química, así como de desarrollar políticas públicas dirigidas a prevenir el consumo de drogas sintéticas y mitigar sus impactos en la salud pública.

Palabras Clave: *Neumonía. Neumonitis. Drogas ilícitas. Abuso de sustancias.*

INTRODUCTION

Pneumonia is an inflammation of the lungs often associated with bacterial, viral, or fungal infections. However, beyond infectious agents, non-infectious factors such as the inhalation of toxic substances can trigger severe pulmonary inflammatory processes. The use of inhaled drugs represents a significant risk factor for lung diseases due to their deleterious effects on the respiratory epithelium, impairing pulmonary defense mechanisms and increasing susceptibility to infections, including pneumonia.[1,2]

Community-acquired pneumonia (CAP) remains one of the leading causes of global morbidity and mortality. According to data from the Department of Informatics of the Brazilian Unified Health System (DATASUS), in 2023, there were 655,827 hospitalizations due to pneumonia and 65,109 related deaths across all regions of Brazil. This scenario underscores the need for studies that investigate aggravating factors of CAP, including the influence of illicit substance use.[3,4]

Chemical pneumonitis is an acute form of pulmonary inflammation that results from the inhalation or aspiration of toxic substances, such as vapors, gases, fumes, or irritating liquids.[5] Inhaled drugs like cocaine, crack, heroin, and volatile solvents can cause direct damage to the upper and lower airways, compromising ciliary function and reducing the respiratory system's ability to eliminate pathogens. This facilitates the development of severe pulmonary infections, including viral and bacterial pneumonia.[6,7]

In recent years, the emergence of synthetic drugs from the K class (such as K2, K4, K9, Spice, and K12) has posed a new challenge to public health. These substances, initially developed for pharmacological research, are often marketed as cannabis alternatives and misleadingly referred to as "synthetic marijuana." However, their mechanisms of action and effects on the body are significantly different and often more potent and dangerous.[8] The drug K9, in particular, has been linked to several serious adverse effects, including respiratory, cardiovascular, and neurological complications.[9]

Given this scenario, this study aimed to report a case of chemical pneumonitis associated with the use of the synthetic drug K9, emphasizing its relevance in differential diagnosis and appropriate clinical management. Understanding the respiratory impacts of these substances is essential to improving diagnosis, treatment, and prevention strategies, thereby reducing risks to public health.

CASE DESCRIPTION

A 33-year-old male patient with a history of asthma, anxiety disorder, untreated chronic heart failure, chronic alcoholism, and marijuana, crack, and cocaine use since age 15, with several unsuccessful hospitalizations for chemical dependency treatment and rehabilitation, and recent use of K9.

The patient sought medical care at the emergency room with a history of asthenia, fever, productive cough with purulent sputum associated with progressive dyspnea for 7 days. Due to marked worsening on the date of admission, he was immediately transferred to a general hospital. Upon arrival, the patient was drowsy, confused, tachypneic, with a respiratory rate of 30 breaths per minute, using accessory muscles, and had low oxygen saturation, requiring a reservoir mask at 10 L/min to achieve an oxygen saturation of 92%.

Radiographic images showed diffuse interstitial involvement, alveolar opacities in the middle lung fields and at the right base, as well as an enlarged heart area (Figure 1).

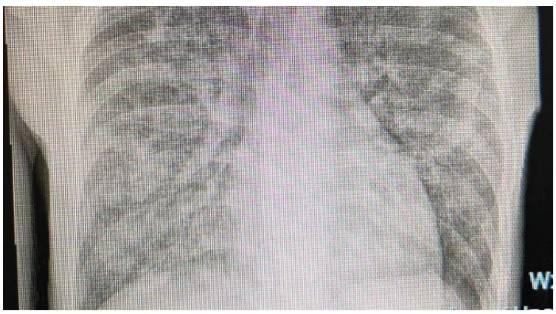

Figure 1. Chest X-ray of the patient at the time care was initiated.

He was transferred to the intensive care unit (ICU), where he required orotracheal intubation and mechanical ventilation. Shortly after sedation began, he developed hypotension, and vasoactive drugs were administered. Due to pulmonary impairment, continuous intravenous infusion of a neuromuscular blocker was required.

Initial diagnostic hypotheses included septic shock of pulmonary origin, secondary to severe community-acquired pneumonia, with possible bacterial, viral, or fungal etiology. Severe pneumonia caused by *Mycobacterium tuberculosis*, SARS-CoV-2 pneumonia (Covid-19), and congestive heart failure (profile C) were also considered as differential diagnoses.

Additional tests were performed, including complete blood count, blood culture, urine culture, tracheal culture, smear test for BAAR (3 samples), serology for HIV, VDRL, HbsAg, Anti-HCV, Covid-19, influenza, all with negative results, as well as imaging tests such as X-ray, CT scan, and chest ultrasound. On February 10th, empirical treatment with levofloxacin, oxacillin, and fluconazole was initiated, and the patient remained on these medications for 10 days.

Given that all tests returned negative and considering family-reported information regarding the patient's long-term drug use — with recent use of the synthetic

substance K9 — the working diagnosis of chemical pneumonitis associated with K9 inhalation was established. Corticosteroids were administered at anti-inflammatory doses, leading to an improvement in hypoxia and facilitating progressive weaning from mechanical ventilation.

The patient remained in the ICU for 17 days, with 11 days of invasive mechanical ventilation. After extubation, while still in the ICU, he developed hyperactive delirium and withdrawal syndrome. He was later transferred to the internal medicine ward, where he remained hospitalized for another 7 days, showing significant improvement in both pulmonary function and substance withdrawal symptoms. He was discharged from the hospital and referred to a rehabilitation clinic (Figure 2).

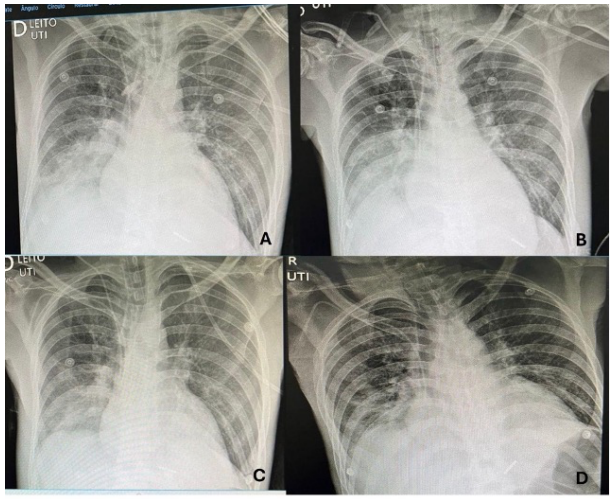

Figure 2. Sequence of chest X-rays showing improvement in the patient's clinical condition.

The study was conducted in accordance with the ethical standards outlined in Resolutions 466/2012 and 580/2018 of the Brazilian Ministry of Health. It was approved by the Research Ethics Committee (CEP) on July 28, 2017, under opinion no. 2.190.929 and CAAE (Certificate of Presentation for Ethical Consideration) no. 70623317.7.0000.5581.

DISCUSSION

Community-acquired pneumonia (CAP) is a common pulmonary infection caused by a variety of pathogens, including bacteria, viruses, and fungi. During the Covid-19 pandemic, there was a significant increase in CAP cases, often complicating the differentiation between SARS-CoV-2 infection and other etiologies.[10] Additionally, the strain on healthcare systems underscored the need for accurate diagnoses to optimize patient management and reduce hospital costs.[11]

The diagnosis of CAP is primarily based on clinical and radiological evaluation, with chest radiography being a key diagnostic tool. However, distinguishing CAP from Covid-19 can be challenging due to overlapping symptoms, such as fever, cough, and dyspnea. Although specific signs, like anosmia and ageusia, may suggest a viral origin, these can also be present in CAP.[8] In the present case, the absence of identifiable pathogens combined with a history of synthetic drug use (K9) pointed toward a diagnosis of chemical pneumonitis.

Chemical pneumonia related to illicit drug use — especially via inhalation or intravenous routes — constitutes a form of toxic pneumonitis caused by the inhalation or aspiration of lung-irritating substances. In such cases, the inflammatory response is initially sterile, triggered by chemical compounds found in substances like crack, methamphetamine, heroin, or K9. However, bacterial infections often overlap, especially in chronic and immunocompromised individuals, which characterizes secondary CAP. The main associated etiological agents include *Streptococcus pneumoniae*, *Staphylococcus aureus* (including MRSA), *Klebsiella pneumoniae*, and, in more severe cases, *Pseudomonas aeruginosa* and oral anaerobes, especially in contexts of aspiration with decreased level of consciousness. Proper identification of the etiology — chemical, infectious, or mixed — is essential to guide treatment, which may range from ventilatory support and anti-inflammatory measures to specific antibiotic therapy.[11,13,14]

The use of inhaled drugs such as cocaine and crack is a recognized risk factor for pulmonary injuries, including chemical pneumonitis, bronchospasm, and alveolar hemorrhage.[9] However, the patient had chronic use of these substances without previous severe respiratory episodes, suggesting a possible specific effect of K9 in exacerbating the condition. K9 and other synthetic cannabinoids can trigger severe pulmonary inflammatory reactions, leading to the need for intensive ventilatory support.[16]

The most common pathogens associated with CAP include *Streptococcus pneumoniae*, followed by *Haemophilus influenzae*, *Mycoplasma pneumoniae*, and respiratory viruses such as influenza and SARS-CoV-2. Immunocompromised individuals, such as those with untreated HIV, are at higher risk for opportunistic infections like pneumocystosis and tuberculosis.[17] The use of illicit drugs is also associated with increased susceptibility to respiratory infections, due to both chronic immunosuppression and exposure to unsanitary environments.[11]

The impact of novel synthetic drugs like K9 remains poorly understood in the scientific literature. Reports suggest these substances can provoke severe pulmonary reactions, leading to more extended hospital stays and high consumption of healthcare resources.[18] Studies show that illicit drug use is on the rise, with a global increase of 23% over the past decade.[3,4,11] In Brazil, research indicates that millions of individuals have used

illicit substances, with marijuana and cocaine being the most prevalent.[11,18]

The burden on the healthcare system is significant, as patients with chemical pneumonitis often require intensive ventilatory support, increasing demand for ICU beds and specialized resources. Therefore, implementing preventive strategies and public policies aimed at reducing the use of these substances is essential to prevent further deterioration in public health.[16,18]

This case highlights the importance of recognizing new synthetic drugs such as K9 in the differential diagnosis of CAP in young patients presenting with severe respiratory symptoms and a history of substance abuse. Early diagnosis can enable more efficient clinical management and avoid unnecessary hospital costs. Furthermore, it underscores the need for healthcare professionals to be trained to recognize clinical and radiological patterns suggestive of synthetic drug-related chemical pneumonitis, allowing for more targeted and effective treatment.[11]

Finally, a warning must be issued to health authorities to prepare for a potential rise in hospital admissions related to this new class of drugs. Epidemiological surveillance measures, awareness campaigns, and investments in professional training are essential to mitigate the impact of these substances on the healthcare system.

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AUTHORS' CONTRIBUTIONS

André Zitelli contributed to the bibliographic research, writing of the abstract, introduction, methodology, discussion, interpretation and description of the results, conclusions, review, and acquisition of funds. **Álvaro Henrique Volpini Vilera** contributed to the bibliographic research, writing of the abstract, introduction, methodology, discussion, interpretation and description of the results, conclusions, and review. **Larissa Pereira da Silva** contributed to the bibliographic research, writing of the abstract, introduction, methodology, discussion, interpretation and description of the results, conclusions, review, and data collection for the report. **Luis Gustavo Durante Bacelar** contributed to project management, writing of the abstract, methodology, interpretation of the results, conclusions, review, and formatting of references. **Luiz Paulo Furtado Pompolim** contributed to project management, fund acquisition, bibliographic research, and review. **Victor de Albuquerque Orsolin** contributed to the bibliographic research, writing of the abstract, introduction, methodology, discussion, interpretation and description of the results, conclusions, review, and translation. **Silvia Nunes Szente Fonseca** acted as advisor, contributing with corrections and editing.

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

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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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Letter to the Editor

Bacilão vacilão: an amigurumi mascot for tuberculosis education

Bacilão vacilão: uma mascote de amigurumi para educação em tuberculose
Bacilão vacilão: una mascota amigurumi para la educación sobre la tuberculosis

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Corresponding author:
E-mail: dienefer_bierhals@hotmail.com
Address: General Osório Street, s/n – Center, Rio Grande, Rio Grande do Sul, Brazil.

Mariana Quaresma de Souza[1,2]
Dienefer Venske Bierhals[1,2]
Yasmin Castillos das Neves[1,2]
Jéssica Quaresma da Rosa[1]
Ana Júlia Reis[1]
Andrea von Groll[1,2]
Pedro Eduardo Almeida da Silva[1,2]
Ivy Bastos Ramis[1,2]

[1]Medical Microbiology Research Center, Federal University of Rio Grande, Rio Grande, Rio Grande do Sul, Brazil.
[2]Postgraduate Program in Health Sciences, Faculty of Medicine, Federal University of Rio Grande, Rio Grande, Rio Grande do Sul, Brazil.

Health education and promotion actions are essential to raise awareness among the population regarding self-care, and directly contribute to improving quality of life. These initiatives play a relevant role in controlling infectious diseases, such as tuberculosis (TB).[1] Brazil has one of the highest TB burdens in the world, and in 2023, approximately 80 thousand new cases of the disease were estimated.[2,3] Thus, national health education strategies are aligned with the "*Plano Nacional pelo Fim da TB*" and the "*Programa Brasil Saudável – Unir para Cuidar*" of the Ministry of Health. Since TB is a disease associated with social determinants, with higher prevalence in people with low income and lower education levels, and those in vulnerable situations, such as those deprived of liberty, in a state of homelessness, and living with HIV/Aids, strategies are also aligned with the social purpose of disease control.[2]

Seeking a playful and accessible way to address TB in health education actions, the Núcleo de Pesquisa em Microbiologia Médica da Universidade Federal do Rio Grande (NUPEMM-FURG), in Rio Grande, Rio Grande do Sul (RS), developed a mascot named "Bacilão Vacilão." The mascot was made of crochet, following the amigurumi style. The term amigurumi means "crochet doll," and its use has already been demonstrated as promising in health education.[4] The amigurumi developed by NUPEMM-FURG was inspired by the bacillus *Mycobacterium tuberculosis*, the etiological agent of TB, when visualized by microscopy, after Ziehl-Nielsen staining. Its pink color, increased size, and humanized aspects were designed to visually attract the public. (Figure 1).

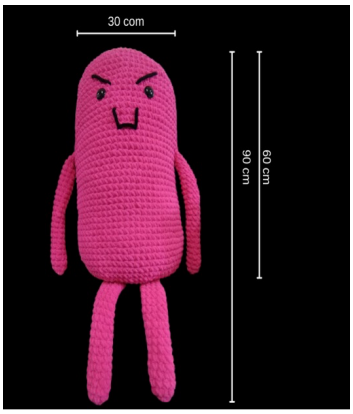

Figure 1. Illustrative image of the mascot "Bacilão Vacilão," highlighting its dimensions, colors and specific shapes used for educational purposes, in Rio Grande, Rio Grande do Sul, 2024.

Strategies involving the use of text, illustrations, and audiovisual content can be used to present the main concepts related to TB as these can be disseminated through social networks or demonstrated in health promotion actions. The amigurumi mascot can assist in explaining the etiology of the disease and the transmission of the bacillus, thereby facilitating the popularization of basic information about TB. "Can TB be transmitted?" From a simple question and with the help of Bacilão Vacilão, a dialogue can be developed starting with what a bacterium is and how to see it under the microscope. This can be extended to how *M. tuberculosis* affects the lungs and open up explanations about coughing as one of the main symptoms of the disease, for example. However, we emphasize that so far, the use of the amigurumi technique for this purpose has not been reported, with "Bacilão Vacilão" being an innovative tool that can be replicated in different scenarios.

Currently, Bacilão Vacilão is being used by NUPEMM-FURG in actions with the local community in the municipality of Rio Grande, which is a priority for TB control in RS. With 40 new TB cases per 100 thousand inhabitants, this state has a higher incidence rate than the national average (37 new TB cases per 100 thousand inhabitants). Rio Grande, in turn, is among the ten priority municipalities for disease control in RS, with 71.4 TB cases per 100 thousand inhabitants in 2023.[2,6] Despite this scenario, health education actions focused on TB occur infrequently in the state.[1]

This letter to the editor presents an innovative and didactic tool for popularizing knowledge about TB and recognizes the need to strengthen health education and promotion actions focused on the disease. Previously, Bacilão Vacilão was used in extension and health promotion actions in public schools in the municipality of Rio Grande and in activities aimed at undergraduate students at FURG, along with the "Ciência na Cidade, Ciência na Vida" program of the university itself. Additionally, the mascot was presented to teachers of Youth and Adult Education – EJA in the southern region of the state through the "Quebrando Barreiras - Comunidade Carcerária contra Tuberculose e Hepatite C" project, which is promoted by the Núcleo de Pesquisa e Extensão com Foco no Sistema Prisional – NUPESISP, of the Universidade de Santa Cruz do Sul – UNISC. The mascot was received with enthusiasm in these different scenarios, consequently promoting dialogues about TB.

As future perspectives, the use of the mascot with educators in actions aimed at elementary and high school students in public and private schools in the southern region of RS is highlighted. The children and adolescents reached by the actions to be developed can act as multipliers of knowledge about TB in their social circles. Additionally, actions in schools aim to reach the adult public through Youth and Adult Education – EJA in prison establishments, as this is a population at risk of TB development.

The use of the mascot can also serve as inspiration for actions at the national level, thus resulting in the creation of similar prototypes and encouraging health education. Furthermore, the proposed mascot is the

result of an extension project (EXT – 2114) developed at FURG and reflects the responsibility of researchers engaged in combating TB to adapt their knowledge about the disease so that it can be disseminated and understood by the community. Thus, university extension, which is one of the pillars of the teaching-research-extension triad of Brazilian higher education, acts in the development of educational practices through the integration of technical-scientific knowledge from academia with popular knowledge, and is an important tool for health promotion.[7]

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AUTHORS' CONTRIBUTIONS

Mariana Quaresma de Souza conception, design, and writing of the article. **Dienefer Venske Bierhals** conception, design, and writing of the article. **Yasmin Castillos das Neves** conception, design, and writing of the article. **Jéssica Quaresma da Rosa** conception, design, and writing of the article. **Ana Júlia Reis** planning, review, and final approval of the article. **Andrea von Groll** planning, review, and final approval of the article. **Pedro Eduardo Almeida da Silva** funding acquisition, planning, review, and final approval of the article. **Ivy Bastos Ramis** funding acquisition, planning, review, and final approval of the article.

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