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# HUMAN BRUCELLOSIS IN TOCANTINS, BRAZIL: SPATIOTEMPORAL DISTRIBUTION AND EPIDEMIOLOGICAL PROFILE
# BRUCELOSIS HUMANA EN TOCANTINS: ANÁLISIS ESPACIOTEMPORAL Y PERFIL EPIDEMIOLÓGICO

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**ABSTRACT**

Human brucellosis is a zoonotic disease, caused by gram-negative bacteria in the genus Brucella, which can have severe complications, including endocarditis and testicular infection. Human brucellosis, due to its common symptoms with other infectious diseases, is often under-surveilled and under-diagnosed. This study examines the incidence of brucellosis in Tocantins, Brazil, its spatiotemporal pattern and demographic, occupational, and clinical characteristics of human cases. Data was collected following existing laboratory protocols, using serum agglutination test (SAT) with Rose Bengal-stained Brucella. The endemicity of human brucellosis to the region is established, with 223 suspected and 37 confirmed human cases between 2012-2015 in 6 of 8 state health regions. Incidence of human brucellosis and report of animal cases were significantly linked. This work contributes to filling the gap of knowledge of this neglected disease in Brazil and constructs a better picture of the effects and epidemiology of human brucellosis in the South American region. Future work should focus on increasing diagnostic capability of human brucellosis with an improved surveillance system, as this will provide for more effective treatment of an underreported disease that is growing in incidence with debilitating, severe long-term complications.

**Keywords:** Brucella; occupational exposure; northern Brazil; agricultural worker.

**RESUMEN**

La brucelosis humana es una enfermedad zoonótica, causada por bacterias gramnegativas del género Brucella, que puede tener complicaciones graves, incluyendo endocarditis e infección testicular. La brucelosis humana, debido a sus síntomas comunes con otras enfermedades infecciosas, a menudo es subvigilada y subdiagnosticada. Este estudio examina la incidencia de la brucelosis en Tocantins, Brasil, su patrón espaciotemporal y las características demográficas, ocupacionales y clínicas de los casos humanos. Los datos se recopilaron siguiendo los protocolos de laboratorio existentes, utilizando la prueba de aglutinación sérica (SAT) con Brucella teñida con rosa de Bengala. Se estableció la endemicidad de la brucelosis humana en la región, con 223 casos humanos sospechosos y 37 confirmados entre 2012 y 2015 en 6 de las 8 regiones sanitarias estatales. La incidencia de la brucelosis humana y el informe de casos animales estuvieron significativamente vinculados. Este trabajo contribuye a completar el conocimiento sobre esta enfermedad desatendida en Brasil y ofrece una mejor perspectiva de los efectos y la epidemiología de la brucelosis humana en la región sudamericana. Las futuras investigaciones deberían centrarse en aumentar la capacidad diagnóstica de la brucelosis humana mediante un sistema de vigilancia mejorado, ya que esto permitirá un tratamiento más eficaz de una enfermedad subnotificada cuya incidencia está aumentando, con complicaciones debilitantes y graves a largo plazo.

**Palabras claves:** Brucella; exposición laboral; norte de Brasil; trabajador rural.

## INTRODUCCIÓN

Brucellosis is the most common zoonotic disease worldwide that affects both humans and animals. Human brucellosis, caused by Brucella spp., begins with its most frequently expressed symptoms including fever, chills, headaches, sweating and weight loss, which closely mirror those of other infectious diseases [1-3]. However, severe complications of brucellosis are not rare, and can include highly debilitating and chronic conditions such as endocarditis, testicular infection, joint, muscle, and back pain [4].

The impact of the disease and its severe complications are also compounded by the high incidence of human brucellosis, which is primarily linked to the number of different Brucella species, including B. abortus, B. suis, B. neotomae, B. ovis, and B. canis, each of which has its own distinctive epidemiological features [1, 5]. Zoonosis exhibits diverse transmission routes, including food, occupational exposure, recreation, travel, and bioterrorism [6, 7]. Human brucellosis incidence is notably positively correlated with animal brucellosis, emphasizing the interconnectedness requiring comprehensive public health strategies [8].

The incidence of human brucellosis, however, has variations in reported frequency, in part due to a common problem of underreporting and low rates of case confirmation [2]. This underreporting phenomenon stems partially from the similarity of the symptoms of human brucellosis to other zoonotic diseases, usually endemic to the region of study [9]. Furthermore, information on the geographic distribution of cases of human brucellosis in Sub-Saharan Africa, Central, South-East Asia, and South America is limited in comparison to data regarding clinical manifestations of the zoonosis, including Brazil [9, 10]. This suggests a poor brucellosis surveillance system in these regions [9, 11].

The state of Tocantins is located in northern Brazil, and its 139 municipalities holds a population estimated to total 1,511,460 inhabitants [12]. One of the main economic activities in Tocantins is agriculture, and a large proportion of land (roughly 39.4% of the state, which covers approximately 278,000 km2) is devoted such agricultural and pastoral practices [13]. Animal brucellosis is considered a zoonotic disease endemic to Brazil, and this reliance on cattle farming suggests occupational and environmental risk-increasing activities for infection of human brucellosis [14].

In Tocantins, cases of human brucellosis have been reported annually since 2008, and human brucellosis has gained status of compulsory notification since 2015. This signifies more comprehensive data availability regarding surveillance, distribution, and transmission of the disease, especially in comparison to the majority of other states in Brazil in which only outbreaks of human brucellosis are required to be reported and investigated.

Here, we report incidence of brucellosis in Tocantins in a spatial and temporal sense by examining demographic, occupational, clinical, and risk-increasing activities between 2012 and 2015.

## MATERIALS AND METHODS

The population analyzed consisted of the confirmed cases of human brucellosis reported in Tocantins between the years of 2012 and 2015. Demographic, occupational, and patient data was collected and provided by various Brazilian government institutions, including the State Department of Health of Tocantins (SES-TO - Secretaria de Estado da Saúde do Tocantins), through its Advisory Committee on Poisonous Animals and Zoonoses (AAPZ - Assessoria de Animais Peçonhentos e Zoonoses), the Brazilian Institute of Geography and Statistics (IBGE - Instituto Brasileiro de Geografia e Estatística), the Ministry of Agricultural Livestock and Supply (MAPA - Ministério da Agricultura Pecuária e Abastecimento), and the Agricultural Defense Agency of Tocantins (ADAPEC-TO - Agência de Defesa Agropecuária do Tocantins). AAZP is the technical branch responsible for the epidemiological investigation and monitoring of human brucellosis cases in Tocantins and, for that, utilizes the Notification Information System of Disease (SINAN - Sistema de Informação de Agravos de Notificação) and the Records of Investigation of Human Brucellosis (FIBH - Fichas de Investigação de Brucelose Humana).

The existing surveillance protocols for human brucellosis diagnoses are also standardized by each state, leading to differences in effectiveness of diagnoses. In Tocantins, following the Normative Instruction # 10/2017, the utilized method is a serum agglutination test (SAT) with Rose Bengal-stained Brucella antigen, through qualitative and semi-quantitative analyses, associated to symptomatology. SAT tests, polymerase chain reaction (PCR) and immunoassays, which are confirmatory tests, are not available in the network of public health laboratories in Tocantins to diagnose human brucellosis.

The data were analyzed quantitatively, and statistical analyses used to verify existence of significant associations between the occurrences of brucellosis in both humans and animals in the municipalities of Tocantins, through Table 2x2, available at the OpenEpi site, and with the calculation of the Odds Ratios, with a 95% confidence interval. For the spatial and temporal descriptions of the cases of the disease, the digital cartographic database of Tocantins, contained in the ArcGis software (version 10.3.1) of the Department of Planning of Tocantins (Secretaria de Planejamento do Tocantins), made available for use by SES-TO, was used.

This study was submitted for analysis by the Ethics Committee of the Institute of Collective Health of the Federal University of Bahia (ISC/UFBA - Instituto de Saúde Coletiva da Universidade Federal da Bahia), and was approved in accordance with Decision No. 1,929,504, dated February 16, 2017, and also by the Health Education Management Coordination of the Tocantinense School of the SUS, SES-TO, as recommended by Ordinance No. 796/2014.

## RESULTS

Between 2012 to 2015, 223 suspected cases of the disease were reported in 59 of the 139 municipalities in the state Tocantins. A total of 37 cases of human brucellosis were confirmed by laboratory analysis (Fig. 1). Most of the positive individuals were male (75.7%), between the ages of 20 and 49 (64.9%), educated up to a high school level (72.7%), of mixed race (70.3%), and lived in urban areas (78.4%) (Table 1). Data on the symptoms presented by the clinical cases

is present in Appendix B; with weakness (23/35, 65.7%), fever (22/35, 62.8%), headache (19/35, 54.3%), malaise (19/35, 54.3%) and tiredness (18/35, 51.4%) being the most frequent symptoms. Testicular pain was reported by 4 of the 28 male patients.

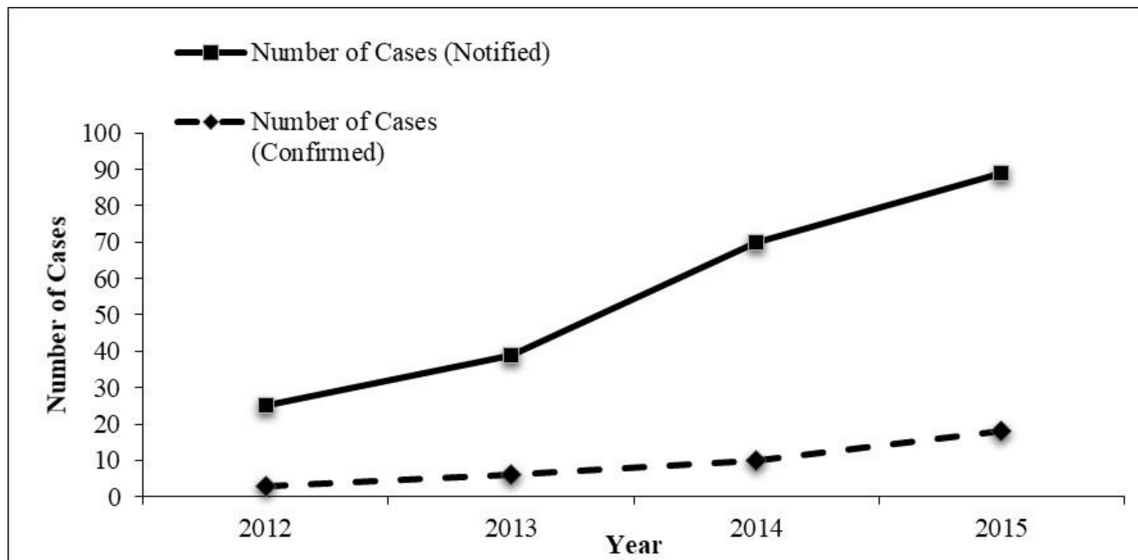


***Figure 1.*** *The relationship between the number of cases reported in the SINAN system and confirmed cases of human brucellosis per year in the state of Tocantins, 2012 to 2015.*

The distribution of the confirmed cases and incidence of human brucellosis by health regions and municipalities of residence in Tocantins are as seen in Figure 2 and Appendix B. The distribution of the disease occurred in 6 of the 8 health regions and in 14 of the 139 municipalities of Tocantins. The regions of Norte Araguaia and Cantão were the ones with the highest incidence. The northern region of Araguaia was the only one that confirmed cases of the disease in all the years studied and had the highest concentration of confirmed cases (62.1%, or 23 out of the 37 total cases) (Appendix B).

Figure 2 shows the annual spatiotemporal distribution per 100,000 inhabitants of the municipalities with cases of human brucellosis, occurring from 2012 to 2015, as well as the correlation between municipalities with confirmed human cases, presence of slaughterhouses, and municipalities with confirmed cases of bovine brucellosis. When comparing the dynamics of the occurrence of animal brucellosis with human brucellosis, of the 36 (26%) municipalities with animal brucellosis, 8 (6%) also had cases in humans. Municipalities reporting animal brucellosis were approximately four times more likely to present human brucellosis (OR = 4.62, CI 1.48-14.4).

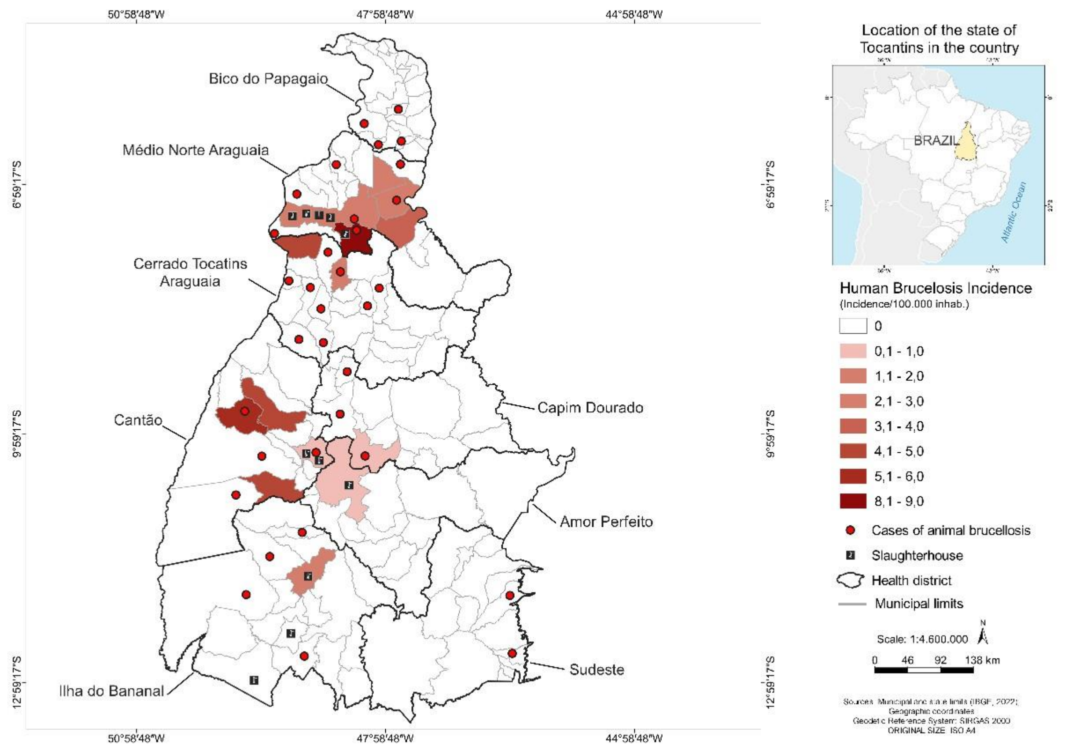


***Figure 2.*** *Spatial distribution of the annual incidence per 100,000 inhabitants of human brucellosis, correlation between municipalities of care and / or notification and slaughterhouses with state or federal inspection services, by municipality of residence, State of Tocantins, 2012 to 2015. Data collected by SINAN and AAPZ/SES-TO; data provided by ADAPEC-TO and MAPA.*

As for the occupation profile of the confirmed individuals, the majority worked in agricultural activities 59.5% (22/37) as farmers, agronomists, slaughterhouse employees, veterinarians, cattle ranchers, and vaccinators (Table 1). Similarly, the most encountered activities for the transmission of human brucellosis were those with contact with tissues and or secretions of animals 51.4% (19/37) and consumption of fresh milk or its derivatives 37.8% (14/37) (Table 1).

*Table 1. Demographic variables and risk-increasing activities. Number and proportions of demographic variables and risk-increasing activities of confirmed cases for human brucellosis, Tocantins, 2012 to 2015.*

| **Demographic variables and risk-increasing activities** | **Number (%)** |
|---|---|
| **Gender (n=37)** | |
| Male | 28 (75.7%) |
| Female | 9 (24.3%) |
| **Age (years) (n=37)** | |
| 1 to 9 | 1 (2.7%) |
| 10 to 19 | 5 (13.5%) |
| 20 to 29 | 9 (24.3%) |
| 30 to 39 | 9 (24.3%) |
| 40 to 49 | 6 (16.2%) |
| 50 to 59 | 3 (8.1%) |
| 60 and above | 4 (10.9%) |
| **Education level (n=33)** | |
| High school | 24 (72.7%) |

| | |
|---|---|
| Post-high school | 9 (27.3%) |
| **Race (n=37)** | |
| Mixed | 26 (70.3%) |
| White | 10 (27.0%) |
| Black | 1 (2.7%) |
| **Type of residence zone (n=37)** | |
| Urban | 29 (78.4%) |
| Rural | 8 (21.6%) |
| **Occupation (n=37)** | |
| Agricultural activities | 22 (59.5%) |
| Other | 9 (24.3%) |
| Children/students | 6 (16.2%) |
| **Risk-increasing activities (n=37) [1]** | |
| Contact with animal secretions and or tissues | 19 (51.4%) |
| Consumption of milk *in natura* or its derivatives | 14 (37.8%) |
| Consumption of poorly cooked meat | 11 (29.7%) |
| Contact with animal vaccine | 11 (29.7%) |

***Observations*: *n*= Number of people in the group with answers.**
[1] it was possible to have more than one response per person.

**DISCUSSION**

The research presented in this analysis of health data has contributed in several ways to filling the gap of knowledge of human brucellosis in northern Brazil: first, it provides further evidence to the endemic nature of human brucellosis in Tocantins; second, it confirmed links of human brucellosis to certain demographic characteristics and occupations.

In the case of human brucellosis, in endemic areas, the incidence may vary from 0.01 to values greater than 200 per 100,000 inhabitants; as the results reflect, human brucellosis is endemic to the state of Tocantins (11). This study also found a significant correlation between the incidence of animal brucellosis and human brucellosis in Tocantins, with municipalities reporting animal brucellosis found to be approximately four times more likely to present human brucellosis. As the endemic nature of animal brucellosis in Brazil has already been confirmed in literature, this finding provides additional support for the endemic nature of human brucellosis in the region (14). As aforementioned, clinical symptoms often mirror those of other infectious diseases, but more severe complications such as testicular edema, conjunctival hyperemia, and testicular pain were also observed within this period (Appendix A).

The Tocantins laboratory diagnosis system primarily utilizes the Rose Bengal Test as a confirmatory test through semiquantitative analysis (expressed in antibody titration), is considered highly effective due to its simplicity, accessibility, affordability, and high specificity, as most other tests are difficult to implement in areas where brucellosis is endemic (15). The test is not technically demanding and easy to interpret, and can be extended to screen a vast number of blood samples, which makes it potentially useful in resource-poor laboratories, particularly in developing regions (16). The state of Tocantins is one of the poorest in Brazil, which reflects in the frailty of the health infrastructure and inadequate provision of laboratory support. Given the precarious situation of the health surveillance and laboratory infrastructure for the public health system in the state of Tocantins, which impedes the performance of more robust tests that would provide unequivocal proof for active infection, the Rose Bengal test represents a fundamental resource for health surveillance in the Global South (15).

However, given the distribution of the confirmed cases, even the use of the Rose Bengal Test suggests low case suspicion and underreporting of human brucellosis, regardless of compulsory notification of incidence in the state. For example, Araguaína maintains the highest number of confirmed cases through the years (with 70.3% of the confirmed

cases) and is the only municipality with a Hospital of Tropical Diseases (HDT), that employs professionals who are familiar with and specializing in the subject (Figure 2, Appendix B). Further, the database within SINAN shows a lack of robust reporting, as eight confirmed cases of human brucellosis were found that were not reported in the system.

Some limitations must be highlighted in our study. The Rose Bengal agglutination test was the only available diagnostic method, which does not allow to infer active infection, as it only detects antibodies [17]. It also has particular issues of low sensitivity, particularly in chronic infections [18], and cross-reactivity [19]. While more advanced tests such as immunological assays (e.g. ELISA) or molecular proofs would provide increased resolution of our data and increase the safety of the inferences, the test still presents adequate sensitivity and specificity for initial epidemiological assessments [15] and represents a fundamental surveillance tool in resource-strained contexts. While our results should be considered with caution, we consider that the tests, the epidemiological profile of the participants and the endemic status of the area provide support for the diagnosis.

## CONCLUSIONS

As mentioned earlier, this study found a significant relationship between animal and human brucellosis. In addition, with the frequency of risk-increasing activities in contact with animals found performed by those confirmed with human brucellosis over the time of the study, this confirmed the occupational character of human brucellosis (Table 1). Additionally, demographic information provided support for occupational character, as men between the ages of 20 to 49 were the most affected demographic group (Table 1).

Considering the links to the variety of strains that have emerged with different epidemiological characteristics, the endemic nature, increase in incidence, and significant ties to animal brucellosis (which is compounded with the frequency of livestock and agricultural occupations in the region) of human brucellosis, in conclusion, suggest that the disease should be monitored with a more comprehensive and effective diagnostic treatment in South America. Future work should focus on increasing diagnostic capability of human brucellosis with a concrete surveillance system, as this will provide for more effective treatment of an underreported, under-diagnosed, and under-treated disease that is growing in incidence with debilitating, and severe long-term complications.


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