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Focal persistence of soil-transmitted helminthiases in impoverished areas in the State of Piaui, Northeastern Brazil

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ABSTRACT

This study aims to describe the prevalence, distribution, and factors associated with soil-transmitted helminthiases (STHs) in rural localities in Piaui, Brazil. Two cross-sectional surveys (n=605 subjects; 172 families) were carried out in order to obtain socio-demographic, anthropometric, spatial and parasitological data. Parasites were evaluated using Kato-Katz and centrifugal sedimentation techniques. Eggs were measured to assess infection with zoonotic Strongylida parasites. Kernel maps were constructed with Q-GIS. The prevalence of hookworm infection was 12.4% (75/605). Other helminthes found were *Trichuris trichiura* (n=1; 0.2%) and *Hymenolepis nana* (n=1; 0.2%). The hookworm positivity rate was significantly lower among subjects who had used albendazole when compared with individuals who had not used anthelmintics or had used antiprotozoal drugs in the last 6 months (8/134 [6.0%] vs. 59/415 [14.2%]; p=0.009). A total of 39/172 (22.7%) families had at least one infected member. The association between the number of dwellers and hookworm positivity in the family was present in a logistic regression multivariate model. Assessment of worm burdens showed 92.2% light, 6.2% moderate, and 1.6% heavy infections. Hookworm eggs (n=34) measured 57.2 - 75.4 µm in length and 36.4 - 44.2 µm in width (mean ± SD = 65.86 ± 4.66 µm L and 40.05 ± 1.99 µm W), commensurate with human hookworms. Hotspots suggest that transmission has a focal pattern. STHs persist in impoverished rural areas in Northeastern Brazil where currently available control strategies (mass drug administration) apparently do not allow the elimination of the infection.

KEYWORDS: Soil-transmitted helminthiases. Hookworm. Prevalence. Epidemiology. Northeast Brazil.

INTRODUCTION

Soil-transmitted helminthiases (STHs) are neglected, poverty-related diseases with higher prevalence in developing countries. These parasites require passage through the soil for the maturation of their infective stages. Among the geohelminths, *Ascaris lumbricoides* and *Trichuris trichiura* are transmitted by ingestion of eggs, while the infective larvae of the hookworms actively penetrate the skin of the host. They cause insidious damage to the host, leading to growth and development deficits and micronutrient deficiencies[1,2]. Global STH prevalence estimates demonstrate that ascariasis is the most common STH, with 819 million infected subjects, followed by trichuriasis with 464 million, and hookworm infection with 438 million[3]. Moreover, hookworm infection is associated with 3.2 million disability-adjusted

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life years (DALYs) and iron-deficiency anemia in tropical regions[4]. The relationship between intestinal helminthiases and malnutrition has been demonstrated. Depending on the worm burden, acute complications occur. Ascariasis is associated with intestinal obstruction, and trichuriasis with rectal prolapse.

In developing countries, the current control strategy for STHs is based on mass drug administration (MDA) in preschool- and school-aged children[5]. MDA has been successfully performed in high-prevalence countries in Asia, sub-Saharan Africa, and Latin America, leading to a reduction in both the prevalence and worm burden[6,7]. In Brazil, MDA is implemented in schools, targets children aged 5-14 years and involves the periodic administration of a single oral dose of 400 mg albendazole by teachers in selected high-risk municipalities. In Brazil, virtually all children aged 5-14 years attend schools. In the municipalities not targeted by school-based MDA programs, anthelmintics are freely distributed by the primary health care system often without performing parasitological analyses. However, this policy presents limitations, such as differences in drug effectiveness against distinct parasite species with a possible reduction in drug activity, development of resistance and reinfections[8-11].

Considering the hypothesis that STH transmission can persist in impoverished areas despite the implementation of control measures, the purpose of this study was to assess STH prevalence, spatial distribution, and associated risk factors in a predominantly rural area of Piaui State, Northeast Brazil, a region where hygiene, access to clean water, and sanitation are inadequate.

MATERIALS AND METHODS

Ethics statement

This study was approved by the Ethics Research Committee of the Oswaldo Cruz Institute/Oswaldo Cruz Foundation (FIOCRUZ), license Nº CAAE: 12125713.5.0000.5248. Written informed consent was obtained from participants or their guardians (parent/guardians provided written informed consent on behalf of any child participants under the age of 18 years). In addition, assent was obtained from participants aged less than 18 years. All data used in the study were anonymized.

Study area

The study was carried out in the municipality of Nossa Senhora de Nazare (NSN) in Piaui State, located in Northeast Brazil (04° 56’ 24” S and 37° 58’ 33” W) comprising an area of 356,264 km^2 (Figure 1) and the population is estimated at 4,556 inhabitants. It is distant from the capital (Teresina) about 140 km and the municipality exhibits a low (0.586) human development index (Brazilian Institute of Geography and Statistics IBGE, census 2010)[12]. The population of the study region is predominantly rural (rural population=70% [3,193/4,556]) living in close contact with domestic sheep,

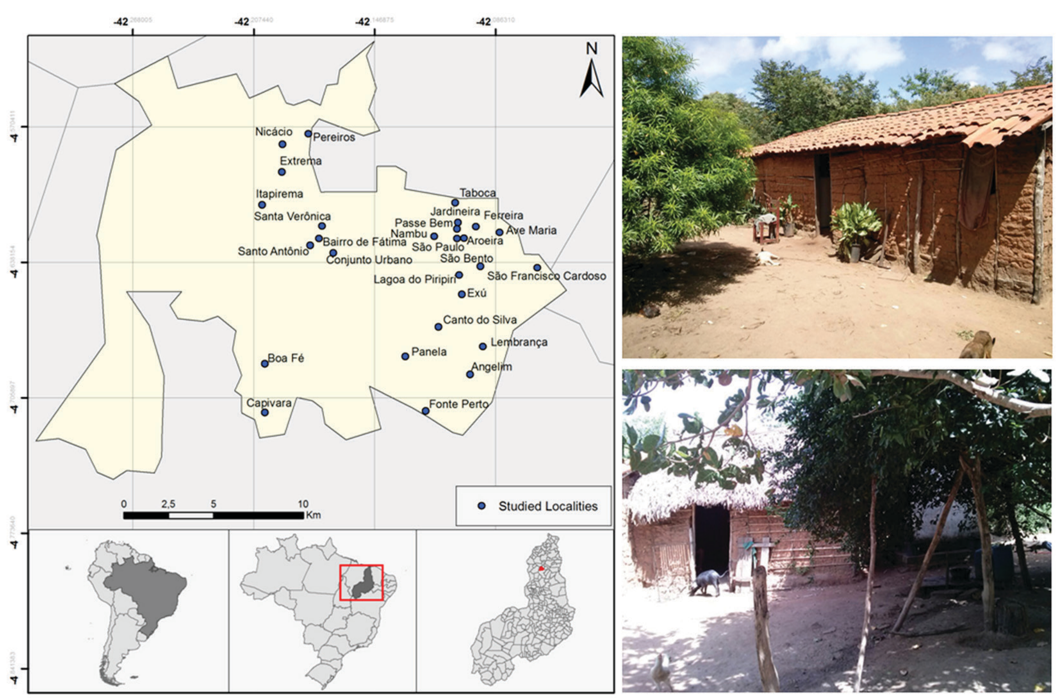

Figure 1 - Geographic location of Nossa Senhora de Nazare in Piaui State and aspect of two visited houses

goats and pigs. The public primary health care system covers the entire local population.

Study design, sampling strategy, and characteristics of sampled population

A cross-sectional survey (27 localities; 172 families/houses; n=605 subjects) was carried out in two steps, the first from August to September 2014 (n=298; 81 families/houses, dry season) and the second from May to July 2015 (n=307; 91 families/houses, rainy season) (Figure 2). In each year, the sampling strategy was designed to include all families with children of the selected localities within the municipality. The localities were selected based on the possibility of access by car, since some are geographically isolated. The number of localities corresponds to 1/3 of the total number in the municipality. This way, in each year we were able to include around 6.5% of the municipality population. Age distribution of the sampled population was as follows: 0 – 14 years, n=217 (35.9%); 15 – 21 years, n=70 (11.6%); 22 – 45 years, n=180 (29.7%); 46 – 60 years, n=75 (12.4%); > 60 years, n=54 (8.9%); unknown age, n=9 (1.5%). Concerning sex, 327/605 (54%) were female. From the sampled population, 134 subjects (22.1%) had used albendazole and 54 (8.9%) had used mebendazole in the last six months. With respect to education, from 373 adults, 77 (20.6%) were illiterate, 226 (60.6%) had up to four years of education, and 70 (18.8%) had five or more years of education. From 172 families, 107 (62.2%) performed open defecation, 27 (15.7%) lived in houses with uncoated clay floor and 38 (22.1%) were extremely poor (monthly per capita familiar income less than 1 USD). The studied municipality is not included in Brazilian MDA programs.

Members of the research team visited the houses in order to distribute plastic bottles without preservatives for the collection of fecal samples and to gather socio-demographic, anthropometric and sanitation data through face-to-face interviews. Fecal samples where recovered 24 h or 48 h after the bottles were distributed, in a second visit and third visit, if necessary. After the study, the research team conducted health education practices, which involved health care (prevention and correct drug administration measures) and talks for schools (data not shown).

Anthropometric measurements

In order to estimate the impact of STHs on the physical development of children, weight and height measurements were obtained from individuals aged up to 14 years. Weight was measured to the nearest 0.1 kilogram using a digital floor scale. Standing height was measured with a steel measuring tape coupled to a steel framing square. Standard deviation scores (Z-scores) (height-for-age [HAZ], weight-for-height [WHZ], and weight-for-age [WAZ]) were calculated using the NutStat module in Epi Info™ 2000 (Centers for Disease Control and Prevention [CDC], Atlanta, USA) and the World Health Organization (WHO) growth chart[13]. Stunting (chronic malnutrition), wasting (acute malnutrition), and underweight (undefined

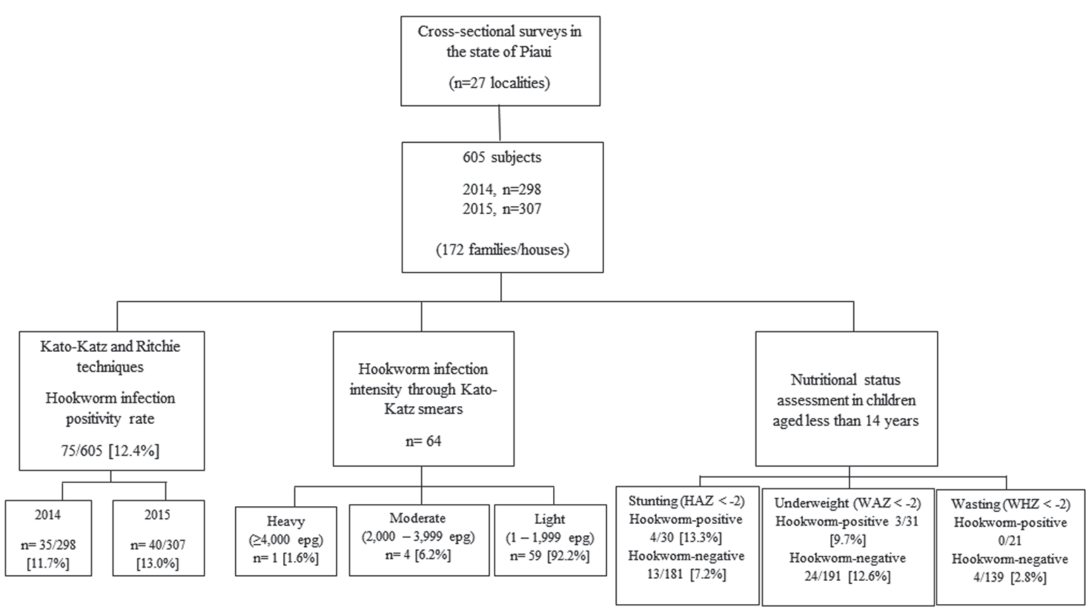

Figure 2 - Flowchart depicting sample size and main results of the cross-sectional surveys performed in Nossa Senhora de Nazare, State of Piaui, Brazil. Legenda: EPG: eggs per gram of feces; HAZ: height-for-age z-scores; WHZ: weight-for-height z-scores; WAZ: weight-for-age z scores

malnutrition) were defined by HAZ, WHZ, and WAZ < -2, respectively, in the reference population[14].

Laboratory procedures

Parasitological examinations were performed by the formalin-ethyl acetate centrifugation method (modified Ritchie technique) and the quantitative Kato-Katz thick smear technique (Helm Test® kit, LabHouse, Belo Horizonte, Minas Gerais, Brazil)[15,16]. The parasitic load was estimated using the Kato-Katz technique (eggs per gram - epg of feces). The hookworm infection intensity was classified into light (1–1,999 epg), moderate (2,000–3,999 epg), or heavy (≥4,000 epg)[17]. The sucrose spontaneous flotation technique was performed for hookworm-positive individuals in order to facilitate egg measurement. An ocular micrometer was used to measure the eggs. These measures were used to aid the differentiation and provide initial information about the possibility of infection with the zoonotic Strongylida *Trichostrongylus* sp. As reference measures, we used the following: i) 63-80 µm × 35-49 µm for *Necator americanus*, ii) 60-77 µm × 35-45 µm for *Ancylostoma duodenale*, and iii) 75-95 µm × 40-50 µm for *Trichostrongylus* sp.[18,19]. The R program v.3.2.3 was used for the descriptive statistics of egg measurements.

The results of the parasitological examinations were delivered to each study participant, and a treatment was performed with a 3-day course of mebendazole (100 mg twice a day) for STHs.

Spatial analyses

The base map was acquired from IBGE (Brazilian Institute of Geography and Statistics). The coordinates of the sampling sites were determined using a hand-held Global Positioning System (GPS) receiver and were recorded in the SAD 69 datum (South American Datum 1969) geodetic coordinate system. For exploration and modeling, the maps were analyzed for spatial point patterns using the Kernel method. A quartic analysis method was used to allow spatial variation in the point densities, evaluating only the first-order effects. The spatial data were analyzed in a (Geographic Information System) (GIS) platform using the open-source (*Quantum* GIS) QGIS (version 2.14.3 Essen) a free and open source geographic information system software.

Statistical analyses

Two distinct analytic approaches were performed. At the individual level, we compared the positivity rates by season, by anthelmintic use, and by sex with Fisher's exact test. Positivity in distinct educational levels and age groups were compared with chi-square test for linear trend. The frequencies of distinct forms of malnutrition (i.e. acute, undefined or chronic, see description below) were compared in the hookworm-positive and hookworm-negative groups of children with Fisher's exact test. At the family level, positivity rates (i.e. at least one positive person in the house) by site of defecation, type of floor, number of inhabitants, presence of extreme poverty, and presence of pigs, goats, sheep and type of soil were compared with Fisher's exact test. A multivariate analysis was performed through logistic regression. In the multiple logistic regression model, the outcome was hookworm positivity. The predictors, assessed simultaneously, were season, number of dwellers living in the domicile, type of floor, type of soil, site of defecation, presence of extreme poverty, and presence of goats, pigs and sheep in the peridomicile. The correlation between the intensity of infection (eggs per gram [epg] of feces) and age was assessed through partial correlation, assessing the Spearman's (Rho) coefficient and its statistical significance. Comparison of egg counts in the rainy and dry seasons were performed with the Kruskall-Wallis test). For all analyses, alpha-level was set at 5% ($p<0.05$). Statistical analyses were performed with SPSS® (IBM Corp., Armonk, NY, USA).

RESULTS

The overall prevalence of hookworm infection was 12.4% (75/605). There was no infection by *Ascaris lumbricoides*. Other helminth infections were found to a lesser extent: *Trichuris trichiura* (n=1; 0.16%) and *Hymenolepis nana* (n=1; 0.16%). The prevalence rates of hookworm infection in the dry (2014) and rainy (2015) seasons were 11.7% (35/298) and 13% (40/307), respectively (p=0.631) (Table 1). Prevalence reached 12.1% and 14.8% among preschool (0 - 5 years-old) and school (6 - 14 years-old) aged children and positivity rates were similar in distinct age groups (Table 1). The positivity rate was similar among males (40/278 [14.4%]) and females (35/327 [10.7%]), p=0.170. In addition, hookworm positivity was not significantly different among adults with less than four study years (illiterate 11/77 [14.3%] and 1-4 study years 31/226 [13.7%] vs. > 4 study years 3/70 [4.3%]; p=0.052; Table 1). The use of antiparasitic drugs up to 6 months prior to this study was evaluated: 188 (31.07%) subjects used anthelmintic drugs (134 [22.14%] used albendazole and 54 [8.9%] used mebendazole), and 267 (44.3%) subjects used antiprotozoal drugs (252 [41.7%] used metronidazole and 15 [2.5%] used secnidazole). The hookworm positivity rate was significantly lower among subjects who had used albendazole when compared with individuals who had not used anthelmintics or had used antiprotozoal drugs in the last 6 months (8/134 [6.0%] vs. 59/415 [14.2%]; p=0.009). Positivity rates in subjects previously treated with mebendazole were not significantly different from those of individuals treated with albendazole (p=0.078).

Table 1 - Hookworm positivity rates in distinct age groups, genders and seasons in Nossa Senhora de Nazare, State of Piaui, Brazil, 2014-2015

	Hookworm positivity rate	*p-value*
Season		
Dry	11.7% (35/298)	0.631
Rainy	13% (40/307)	
*Age in years**		
0-5	12.1% (11/91)	0.144
6-14	14.8% (22/149)	
15-21	19.2% (9/47)	
22-45	10.6% (19/180)	
46-60	12.0% (9/75)	
> 60	7.4% (4/54)	
Unknown	11.1% (1/9)	
*Use of antihelmintics in the last 6 months***		
Albendazole	6.0% (8/134)	0.009
Mebendazole	14.8% (8/54)	
None or only antiprotozoal drugs	14.2% (59/415)	
Unknown	0.0% (0/2)	
Sex		
Male	14.4% (40/278)	0.170
Female	10.7% (35/327)	
Education in adults		
Illiterate	14.3% (11/77)	0.052
1-4 study years	13.7% (31/226)	
> 4 study years	4.3% (3/70)	

*Chi-square for linear trend **Albendazole vs. none or only antiprotozoal drugs

Considering hookworm positivity in the family, a total of 39/172 (22.7%) families had at least one infected member (Table 2). In the univariate analyses, houses with more than four subjects presented higher hookworm positivity when compared to houses with four or less inhabitants. In addition, positivity in families living in houses with an uncoated clay floor and in those families possessing sheep was significantly higher. Positivity was similar in houses situated in sandy and clayey soil (Table 2). The association between the number of dwellers and hookworm positivity in the family was also present in the logistic regression multivariate model (Table 2).

In 85.3% (64/75) of hookworm-positive individuals, the infection intensity could be assessed: 59 (92.2%) had light, 4 (6.2%) had moderate and 1 (1.6%) had heavy hookworm infection intensity. Partial correlation analysis showed higher fecal egg counts in younger subjects, but this was not statistically significant (Rho=-0.202; p=0.101) (Figure 3). The median parasite load was similar in the dry and rainy seasons (288 epg [interquartile range = 72 – 912 epg] vs. 168 epg [48 – 312 epg], p = 0.211).

Hookworm eggs (n=34) measured 57.2 - 75.4 µm in length and 36.4 - 44.2 µm in width (mean ± SD = 65.86 ± 4.66 µm L and 40.05 ± 1.99 µm W), commensurate with human hookworm (Figure 4A and B).

It was observed that 60% of the positive subjects were situated in only 2 of the 27 studied localities (Sao Paulo and Passa Bem) and therefore the spatial distribution of hookworm infection presented a focal pattern. The Kernel density map identified six hotspot areas in the municipality of NSN (Figure 5), representing higher transmission areas that present hookworm prevalence ≥ 20%.

The frequencies of distinct forms of malnutrition were not significantly distinct among hookworm-positive and hookworm-negative subjects (not shown). Nevertheless, the frequency of stunting in hookworm-infected children (4/30 [13.3%]) was almost twice the frequency observed in hookworm-negative children (13/181 [7.2%]), but this was not statistically significant (p=0.207). The proportions of underweight hookworm-positive and hookworm-negative children were 3/31 (9.7%) and 24/191 (12.6%), respectively (p=0.458). The frequency of wasting was 0/21 in hookworm-positive and 4/139 (2.8%) in hookworm-negative subjects (p=0.574).

DISCUSSION

Our results demonstrate a moderate prevalence of hookworm infection in NSN, Piaui State, Brazil. According to the WHO and the Brazilian Ministry of Health, regions with an STH prevalence above 20% are considered to be at higher risk and are included in the MDA programs[20]. The prevalence of STHs in different Brazilian municipalities is largely unknown, and adherence to the MS-funded MDA program is an option of local health authorities. The municipality studied has chosen not to join the MDA program[21]. Retrospective data analyses have estimated that the prevalence of hookworm infection in Brazil has undergone a drastic decrease in the past 20 years, with expected prevalence rates of 1.7%[22] and 2.5%[23]. A previous

Table 2 - Hookworm positivity rates by family (at least one positive subject in the house) in distinct sociodemographic settings in Nossa Senhora de Nazare, State of Piaui, Brazil, 2014-2015

Characteristic	Hookworm Positivity	Crude Odds ratio (95% CI)	*p-value*	Adjusted Odds ratio (95% CI)	*p-value*
Season					
Dry	16/91 (17.6%)	1.85 (0.90-3.83)	0.065	1.57 (0.70-3.48)	0.267
Rainy	23/81 (28.4%)				
Number of dwellers					
≤ 4	15/103 (14.6%)	0.31 (0.15-0.66)	0.001	0.29 (0.13-0.67)	0.003
> 4	24/69 (34.8%)				
Type of floor					
Uncoated floor	11/27 (40.7%)	2.87 (1.20-6.86)	0.017	1.43 (0.52-3.97)	0.480
Ceramic – coated floor	28/145 (19.3%)				
Type of soil					
Sandy	29/127 (22,8%)	1.03 (0.45-2.34)	0.555	1.23 (0.40-3.71)	0.716
Clayey	10/45 (22,2%)				
Site of defecation					
Open defecation	22/91 (24.2%)	1.20 (0.58-2.46)	0.376	1.03 (0.39-2.69)	0.938
Latrine	17/81 (21%)				
*Extreme poverty**					
Yes	8/38 (21.1%)	0.89 (0.37-2.16)	0.501	0.73 (0.27-2.00)	0.551
No	30/131 (22.9%)				
Presence of goats					
Yes	7/34 (20.6%)	0.85% (0.34-20.15)	0.472	1.61(0.52-4.95)	0.402
No	32/138 (26.2%)				
Presence of pigs					
Yes	23/104 (22.1%)	0.92 (0.44-1.90)	0.485	0.85 (0.36-2.01)	0.723
No	16/68 (23.5%)				
Presence of sheep					
Yes	0/21 (0%)	Undefined	0.003	Undefined	0.962
No	39/151 (25.8%)				

* Per capita monthly familiar income < RS$ 70; missing information for one family

work has shown a prevalence of 9.7% in a semiarid region in the state of Piaui in 2000 and 2001[24].

The sociodemographic and environmental determinants of STHs involve interactions between the physical environment (either natural or man-modified) and human behavior[25]. We did not observe a higher positivity of hookworm infection in families that performed open defecation compared to families using latrines (septic tanks). The association between open defecation - a common practice among rural populations - and hookworm infection has been described in other developing countries[26,27]. Interestingly, in our study, open defecation is performed even in dwellings that have a latrine. This suggests that open defecation is, at least in part, culturally determined and not only a consequence of poverty and lack of access to sanitary resources. Children are likely more exposed to infective free-living larvae and tended to present the highest parasite load. In the present study, another risk factor associated with hookworm infection was

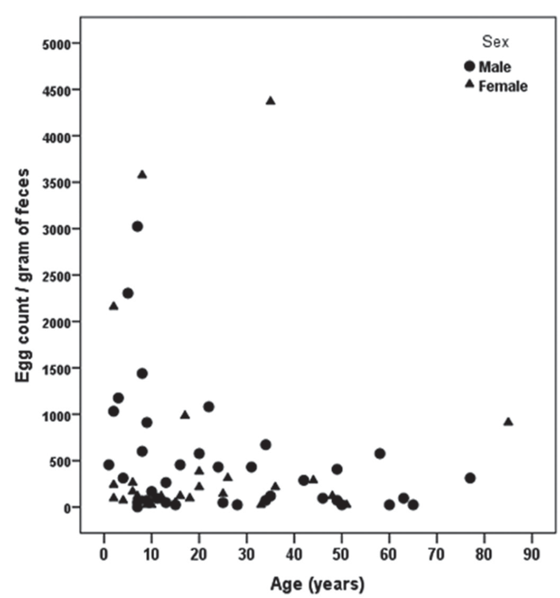

Figure 3 - Scatter plot depicting hookworm egg fecal counts per gram of feces by age

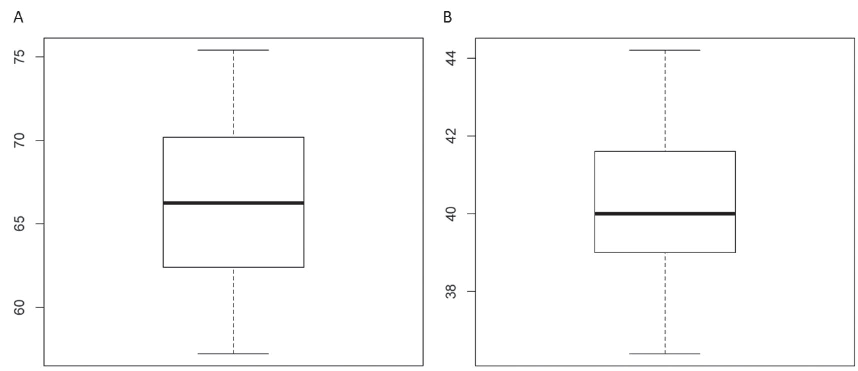

Figure 4 - Boxplots of length (A) and width (B) of hookworm eggs

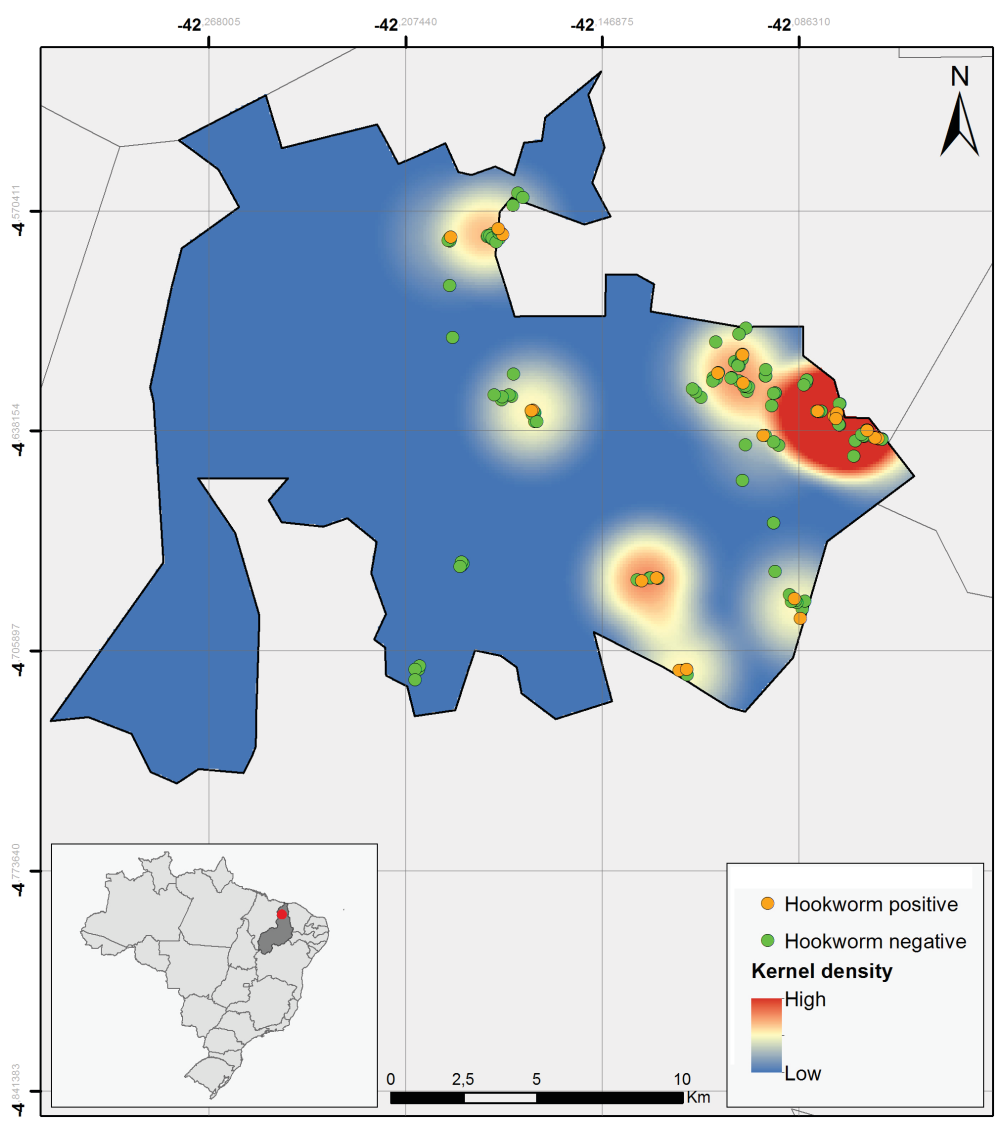

Figure 5 - Mapping on the distribution of hookworm infection (municipalities) depicting hotspots (Kernel density)

living in houses with an uncoated clay floor. Despite we did not identify an association between open defecation and hookworm infection at the family level, the high proportion of open defecation in the studied localities can contribute to the circulation of hookworms. In Nairobi and countries in West Africa, open defecation is intrinsically associated with hookworm infection[28,29]. This sociodemographic scenario enables the persistence of free-living populations of larvae in the peridomestic environment and creates a favorable environment for perpetuating the biological cycle of hookworm and reinfection[30]. In addition, it was observed that hookworm positivity is significantly associated with overcrowding and lower educational status.

In the studied area, the sociodemographic and environmental scenarios favorable to transmission seems to be spatially concentrated, which could explain the focal pattern of spatial distribution of hookworm infection. The majority of hookworm-positive individuals were found to inhabit only a few localities. This suggests that a spatially targeted approach for hookworm interventions, including hookworm surveys, should be prioritized in high-risk areas.

We observed that hookworm infection was homogenously distributed among different age groups pointing to the necessity of expanding the program for adults, as has been discussed in some studies, providing an effective control measure to interrupt transmission[31,32]. No statistically significant associations were observed between stunting, wasting, or underweight and hookworm infection in children. As expected, the prevalence of hookworm infection in individuals who used albendazole (up to 6 months prior to the analysis) proved to be significantly lower. In NSN, the public health service provides free antiparasitic drugs for the treatment of STHs. The treatment regimen used is usually a single 400 mg albendazole dose, although resistance to this drug is already considered a problem and its efficacy against different STH species is variable[33,34].

Human infection with the zoonotic nematode *Trichostrongylus* sp. has been described in Brazil and other countries, especially in rural areas and in populations living in close contact with sheep and goats[35-37]. Although there is little overlap in the length and width measurements, the eggs found in this study were attributable to hookworms. A morphologic study of larvae obtained in coprocultures in addition to the use of molecular taxonomic tools is needed in order to definitively rule out the possibility of misidentifications and infections with zoonotic Strongylida such as *Trichostrongylus* sp.

Currently, there is a consensus concerning a reduction in the STH burden in developing countries, including Brazil[22,38]. Our results are in agreement with this proposal, with the exception of hookworm infection. We observed the absence of *A. lumbricoides* infection and scarce *T. trichiura* infections in NSN. The reduction in transmission of orally ingested STHs can be partially related to improvements in drinking water supplies and efficient primary health services. On the other hand, the persistence of open defecation and inadequate solid excreta elimination can favor the transmission of skin-penetrating STHs, such as hookworm[39]. The results can be generalized to small rural communities in the Brazilian semiarid region with similar socio-environmental characteristics and point to the need of current policies improvements for STH control in economically impoverished rural regions of Brazil.

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AUTHORS' CONTRIBUTION

Conceived and designed the experiments: KJLM, ERCR, BCN, MNB, and FACC. Performed the experiments: KJLM, BCN, JPS, DAC, and AOM. Analyzed the data: KJLM, LHJ, BCN, SCCX, and FACC. Contributed reagents/materials/ analysis tools: ERCR, LHJ, SCCX, MNB. Wrote the paper: KJLM, LHJ, BCN, FACC.

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