Artigo original

Infecções parasitárias intestinais e efeitos adversos em grávidas e seus recém-nascidos em São Tomé e Príncipe: um estudo transversal hospitalar

Intestinal parasitic infections and adverse outcomes among pregnant women and their newborns in São Tomé & Príncipe: a hospital-based cross-sectional study

Infections parasitaires intestinales et issues défavorables chez les femmes enceintes et leurs nouveau-nés à São Tomé et Príncipe: une étude transversale en milieu hospitalier

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Resumo

Introdução: A associação entre infeções parasitárias intestinais (IPI) e resultados adversos da gravidez (ABO) permanece pouco esclarecida, existindo lacunas relevantes de conhecimento. Este estudo teve como objetivo avaliar o impacto das IPI em díades materno-neonatais em São Tomé e Príncipe.

Material e Métodos: Realizou-se um estudo transversal de base hospitalar em grávidas internadas para parto, submetidas a rastreio coproparasitológico durante a gravidez. Foram excluídas as grávidas com infeção por VIH, doença falciforme, malária ou tratamento anti-helmíntico recente. Os dados foram obtidos a partir dos boletins pré-natais, registos neonatais e questionários estruturados. Compararam-se os ABO entre o grupo infetado (n=210) e o grupo não infetado (n=151). As análises de subgrupos incluíram infeções combinadas por helmintas (n=202; 90,9% *Ascaris lumbricoides*), *Schistosoma intercalatum* (n=11) e *Entamoeba histolytic*a (n=7). Foi considerado valor de p<0,05 como estatisticamente significativo.

Resultados: Foram incluídas 361 mulheres (idade média 26,96 anos; DP 7,00). A anemia ocorreu em 39,6% (n=127), a prematuridade em 8,1% (n=26), o baixo peso à nascença (BPN) em 14,9% (n=48) e o óbito fetal em 2,5% (n=8) dos casos. Não se observaram diferenças estatisticamente significativas nas taxas de anemia, prematuridade, BPN ou óbito fetal entre os grupos monoparasitado e não infetado (p=0,182; p=0,175; p=0,07; p=0,275, respetivamente). A prevalência de BPN foi inferior no grupo infetado por helmintas (11,7%) face ao grupo não infetado (19,2%), embora sem significância estatística (p=0,067).

Conclusões: Não foram identificados efeitos adversos significativos associados às IPI em mulheres grávidas. O Ascaris *lumbricoides* foi o parasita mais prevalente e observou-se uma tendência para menor incidência de BPN nas mulheres infetadas. O tratamento anti-helmíntico rotineiro durante a gravidez deve ser utilizado com precaução, dado que infeções assintomáticas podem conferir benefícios imunológicos. A persistência de esquistossomose indica que as declarações de eliminação são prematuras, sendo recomendada a quimioprofilaxia preventiva também em mulheres em idade reprodutiva.

Palavras-chave: *Ascaris lumbricoides*; *Schistosoma intercalatum*; *Entamoeba histolytica*; anemia materna; resultados adversos da gravidez; morte fetal; parto prematuro; baixo peso à nascença.

Abstract

Introduction: The link between intestinal parasitic infections (IPIs) and adverse birth outcomes (ABOs) during pregnancy remains unclear, with significant knowledge gaps. This study aimed to assess the impact of IPIs on maternal-neonatal-dyads in Sao Tome & Principe.

Materials and Methods: A hospital-based study was conducted among women admitted for delivery, who underwent copro-parasitological screening. Women with HIV, sickle cell disease, malaria, or recent anthelminthic treatment were excluded. Data were collected from antenatal cards, newborn records, and structured questionnaires. Outcomes in the infected group (n=210) were compared to those in the non-infected group (n=151). Subgroup analyses included combined-helminths infection (n=202, 90.9% *Ascaris lumbricoides*), *Schistosoma intercalatum* (n=11)

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and *Entamoeba histolytica* (n=7). A p-value<0.05 was considered statistically significant.
Results: A total of 361 women (mean age 26.96 years, SD 7.00) were included. Anaemia was present in 39.6% (n=127), prematurity in 8.1% (n=26), low birth weight in 14.9% (n=48), and stillbirth in 2.5% (n=8) of cases. There were no statistically significant differences in rates of anaemia, prematurity, low birth weight, or stillbirth between the monoparasitic and non-infected groups (p=0.182, p=0.175, p=0.07, p=0.275, respectively). The prevalence of low birth weight was lower in the helminth-infected group (11.7%) compared to the non-infected group (19.2%), though this difference did not reach statistical significance (p=0.067).
Conclusion: No significant adverse outcomes were found in pregnant women with IPIs, with roundworms being most common and low birth weight rates slightly lower among infected mothers. Routine anthelmintic treatment during pregnancy should be used cautiously, as asymptomatic infections may have immunological benefits. Schistosomiasis remains present, suggesting elimination claims are premature and preventive chemotherapy should include women of reproductive age.

Keywords: Soil-transmitted helminths, *Ascaris lumbricoides*, *Schistosoma intercalatum*, *Entamoeba histolytica*, maternal anaemia, adverse birth outcomes, stillbirth, preterm birth, low-birth-weight.

Résumé

Introduction: Le lien entre les infections parasitaires intestinales (IPI) et les issues défavorables de la grossesse (ABO) demeure incertain, avec d'importantes lacunes de connaissance. Cette étude visait à évaluer l'impact des IPI sur les dyades mère-nouveau-né à São Tomé-et-Príncipe.
Méthodes: Une étude transversale en milieu hospitalier a été menée auprès de femmes admises pour accouchement et soumises à un dépistage coproparasitologique. Les femmes présentant une infection par le VIH, une drépanocytose, un paludisme, ou ayant reçu récemment un traitement anthelminthique ont été exclues. Les données ont été collectées à partir des carnets prénatals, des dossiers néonataux et de questionnaires structurés. Les issues du groupe infecté (n=210) ont été comparées à celles du groupe non infecté (n=151). Les analyses de sous-groupes ont inclus des infections combinées à helminthes (n=202 ; 90,9 % *Ascaris lumbricoides*), *Schistosoma intercalatum* (n=11) et *Entamoeba histolytica* (n=7). Une valeur de p < 0,05 a été considérée comme statistiquement significative.
Résultats: Au total, 361 femmes (âge moyen 26,96 ans ; écart-type 7,00) ont été incluses. L'anémie était présente chez 39,6 % (n=127), la prématurité chez 8,1 % (n=26), le faible poids de naissance (FPN) chez 14,9 % (n=48) et la mortinaissance chez 2,5 % (n=8). Aucune différence statistiquement significative n'a été observée entre les groupes monoparasité et non infecté pour les taux d'anémie, de prématurité, de FPN ou de mortinaissance (p=0,182; p=0,175; p=0,07; p=0,275, respectivement). La prévalence du FPN était plus faible dans le groupe infecté par des helminthes (11,7 %) que dans le groupe non infecté (19,2 %), sans signification statistique (p=0,067).
Conclusions: Aucune issue défavorable significative n'a été identifiée chez les femmes enceintes atteintes d'IPI. Les ascaridioses étaient les plus fréquentes et les taux de FPN légèrement inférieurs chez les mères infectées. Le traitement anthelminthique systématique pendant la grossesse doit être utilisé avec prudence, car les infections asymptomatiques peuvent présenter des bénéfices immunologiques potentiels. La schistosomiase reste présente à São Tomé-et-Príncipe, suggérant que les déclarations d'élimination sont prématurées et que la chimioprévention devrait inclure les femmes en âge de procréer.

Mots-clés: *Ascaris lumbricoides*; *Schistosoma intercalatum*; *Entamoeba histolytica*; anémie maternelle; issues défavorables de la grossesse; mortinaissance; naissance prématurée; faible poids de naissance.

Background

Intestinal parasitic infections (IPIs) are neglected tropical diseases (NTDs), with a prevalence of up to 70% among pregnant women [1]. High-burden IPIs are considered an important public health problem in endemic countries, although they are still neglected among pregnant women [1]. IPIs are associated with adverse outcomes, as they might disrupt pregnancy at the maternal-foetal-placental level and impact maternal and neonatal outcomes [2,3]. Despite the potentially enormous at-risk population with IPIs in sub-Saharan Africa (SSA) countries, there is still an important gap in knowledge regarding the pregnancy--related burden of complications that are experienced by women and their offspring [1,4].
The most frequently reported maternal adverse outcomes associated with IPIs are anaemia and poor pregnancy weight, while neonatal adverse birth outcomes (ABOs) are low-birth-weight, preterm birth and stillbirth [1,5]. Moreover, maternal infection might alter the health and immunity of the infant by transferring parasitic antigens and immune effector

molecules, mainly antibodies and cytokines, *in utero* and during lactation [6]. Even today, despite acknowledging that IPIs leave a long-lasting immunological footprint on their hosts, the understanding of which immune mechanisms are altered and how they are changed is limited [6-8]. Some authors reported that babies from IPIs infected mothers can have altered defence against infections, altered response to vaccination and modified risk for allergy and eczema [6-8]. In addition, a causal association remains to be completely proven for the adverse birth outcomes associated with IPIs during pregnancy described in some studies [9-14]. Methodological flaws and heterogeneity between study populations could have interfered with the observed complications found in those studies [15-17]. As an example, most have not used multivariate statistics to split the effects of different intestinal parasite species or other contributing factors.[16] Additionally, most pregnant women from these studies conducted mostly in under-resourced countries, were frequently undernourished, also having other major confounders such as HIV infection, malaria and/or sickle cell anaemia [16]. Therefore, there is still a paucity of data that enables to determine whether the adverse outcomes associated with IPIs reported in the literature are due to confounders, differ with different intestinal parasites or with different causes of maternal anaemia [16].

On the other hand, there is sufficient evidence to suggest that some intestinal parasites are more harmful than others [1,5,16]. For instance, in most cases, long-term helminthic infections are asymptomatic with increased immune Th2 and regulatory responses, suggesting that the helminth has immunomodulatory mechanisms ensuring their survival and chronic existence in the host [6]. Interestingly, those immunological changes associated with helminthic infections resemble those occurring during a successful pregnancy [6]. In addition, only some parasites have a direct role in causing complications such as maternal anaemia, namely, through blood loss, specifically, hookworms, whipworms, and schistosomes [18-21]. In contrast, roundworms or *Ascaris lumbricoides* have an indirect effect, as they interfere with the utilisation of vitamin A, which is required for haematopoiesis [11,22]. Infection with *A. lumbricoides* is known to be mainly asymptomatic, but in high-burden infections, abdominal pain, pulmonary symptoms, and anaemia may surge [2]. Biliary obstruction associated with *A. lumbricoides* infection has been reported to occur in pregnant women due to a rise in progesterone levels that relaxes the motility of the sphincter-of-Oddi [2]. *A. lumbricoides* has also been linked to postpartum haemorrhage related to ascaris coagulopathic properties with increased clotting and partial thromboplastin time [2]. Then again, the shared immunomodulating mechanisms and the alterations in the host's immune response during infection by roundworms might also play a protective role during pregnancy [6].

Regarding human schistosomiasis by trematode worms of the genus *Schistosoma*, the acute infection is usually subclinical, causing mild anaemia [23,24]. In contrast, chronic infection, might trigger an aggressive immune response that can cause granuloma formation and a fibrotic tissue response with complications [23,26]. The placenta-foetus mechanisms of schistosomiasis have also been reported to lead to ABOs, such as low-birth-weight, prematurity, and stillbirth [2,27].

Approximately 90% of *Entamoeba histolytica* infections are asymptomatic or self-limiting [28-30]. Rarely, protozoan-trophozoites, can invade some tissues of the human host with invasive amoebiasis [28-30]. Complications of invasive amoebiasis can range from amoebic dysentery to extraintestinal disease with amoebic-liver-abscesses [28-30]. Alternatively, pregnancy can be a predisposing factor in the reactivation of amoebic infection since the presence of a foetus involves an altered immunological response [30].

Therefore, parasite - direct or indirect - mechanisms (placental inflammation, maternal iron deficiency, and release of proinflammatory cytokines), can lead to a spectrum of maternal-placental-foetal effects depending mainly on the type of species, the timing of infection and the intensity of infection, as well as coinfection with multiple parasites and maternal comorbidities [1,27,31-33].

All the above considerations lead us to question what the impact of IPIs among pregnant women and their offspring is, in a specific setting, the smallest Central Africa country - Sao Tome & Principe - known to be an endemic country for four NTDs, namely, soil-transmitted helminths (STHs), schistosomiasis (only *S. intercalatum*), lymphatic filariasis and leprosy [34]. Currently, the county's government is committed to achieving NTD control and elimination as a public health problem by 2025 and has developed a Strategic Plan for the Fight Against NTDs 2019-2025 [34-35]. Additionally, there is an ongoing mass drug preventive chemotherapy administration using a triple drug

combination of ivermectin, diethylcarbamazine and albendazole for the elimination programme of *Lymphatic filariasis* [35]. As this programme includes albendazole, which is effective in treating helminthic infections, an additional reduction in the prevalence of helminthic infections is expected in future years [12-35]. However, IPIs in this setting have only been studied among toddlers, preschool children, and school children, missing out on pregnant women and their unborn babies [36-38].

and neonatal mortality and morbidity in Sao Tome & Principe [40,44].

Therefore, in this study the authors go further on from the previous study, filling this gap in knowledge concerning the impact of IPIs among pregnant women and their newborns. Thus, the participants for the current study were recruited from the same pool as the previous study conducted by the authors [39]. We now aimed to analyse ABOs in accordance with IPI status and according to the types of parasite species, such

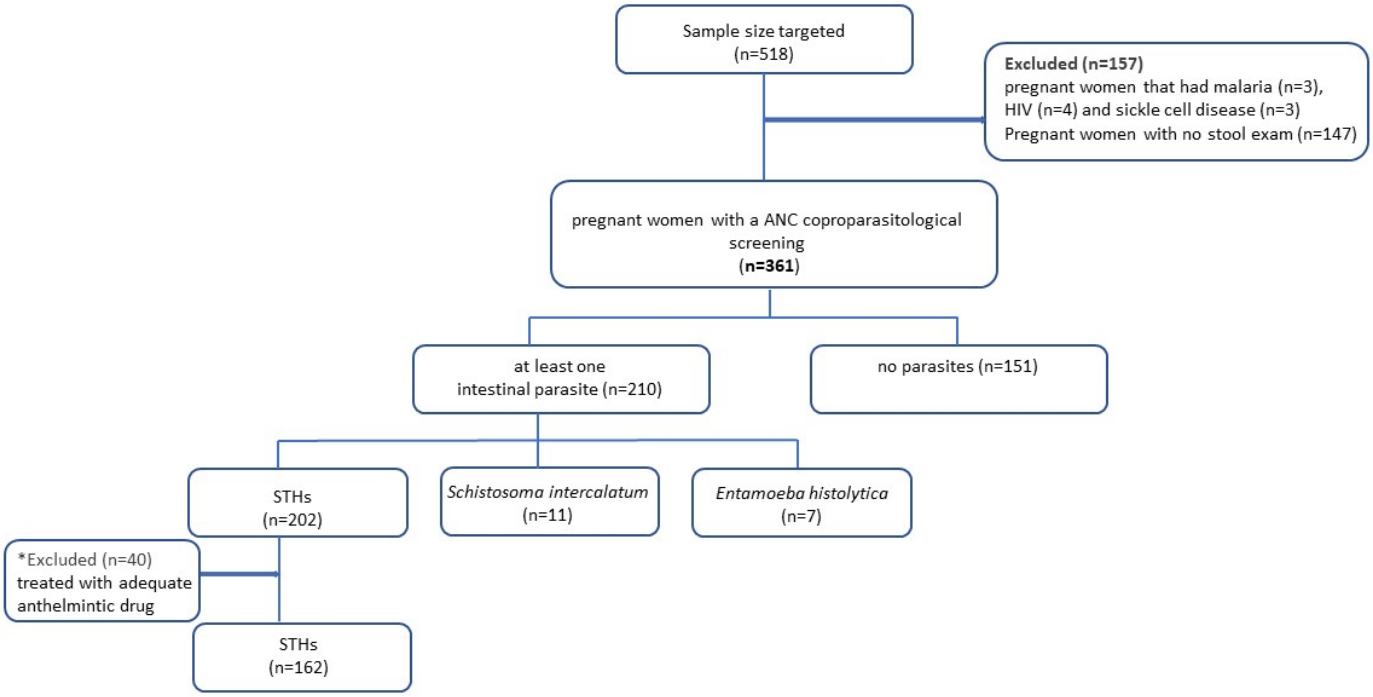

Figura 1: Flowchart of participation in the study
Note: Combined-group for helminths: 191 (90.9%) *roundworms*, 29 (13.8%) *whipworms*, 3 (1.4%) *hookworms* and 1 (0.5%) *Strongyloides stercoralis*. Pregnant women with polyparasitic infections were included. *Only for the adverse maternal and perinatal outcome analysis.
Abbreviations: ANC antenatal care; HIV Human Immunodeficiency Virus; STHs Soil-Transmitted Helminths.

Thus, the authors previously conducted the first study in the country regarding this topic and found a high-IPI overall prevalence of 58.2% (95% CI: 52.9-63.3) among pregnant women, mainly due to roundworm *A. lumbricoides* infection (90.9%), followed by *S. intercalatum* (5.2%) and *Entamoeba histolytica* (3.3%) [39]. *S. intercalatum* terminology will be used since the reports and diagnoses registered in each woman´s ANC pregnancy card are for *S. intercalatum*. However, *Schistosoma guineensis* seems to reflect the current molecular terminology for this parasite species in this setting as recently published, without any differences in the clinical manifestations or transmission previously documented [35].

Additionally, a broader project on neonatal and maternal health has been conducted by the authors, studying the causes and factors associated with perinatal

as helminths, *S. intercalatum* and *Entamoeba histolytica*. Moreover, it should be noted that schistosomiasis among pregnant women, globally, has been poorly understood or investigated [21,45]. To our knowledge, this is the first analysis of *S. intercalatum* infection reports of outcomes in pregnant women and their offspring.

Materials and Methods

Study design and period

A hospital-based cross-sectional analytical study was carried out on maternal-neonatal dyads from pregnant women admitted to the Hospital Dr. Ayres de Menezes (HAM) Maternity Unit for delivery, between July 2016 and November 2018 [39].

Setting

The archipelago has approximately 219 161 inhabitants [46]. The level of poverty is high, with 47% of the population practising open defecation and 69.8% having access to clean and safe drinking water [46]. This study was conducted at the HAM maternity unit, situated in the capital city, which also receives deliveries from nearby communities and referral cases from other health care facilities as it is the only hospital in the country. Approximately 82.4% of all deliveries in the country are performed in this hospital [46].
The IPI prevalence among pregnant women, characterization of antenatal care (ANC) copro-parasitological test results and species found, anthelmintics prescribed for IPIs among pregnant women during ANC and factors associated with IPIs in pregnancy were already analysed and reported in another article [39].

Participants

Eligibility criteria: All women admitted to the hospital for delivery with a gestational age of 28 weeks or more who underwent a copro-parasitological test during the pregnancy period were eligible to be enrolled [39]. Those who gave birth outside the hospital but were admitted because of postnatal complications in the first 12 hours of life were also included in the study [39].
Pregnant women with HIV, sickle cell disorder, malaria and who received anthelminthic treatment during pregnancy were excluded for possible confounding causes of maternal anaemia and birth outcomes [39].
The current study expands upon the previous one by including additional measures related to specific aspects being examined, namely the occurrence of adverse birth outcomes. Pregnant women with an IPI were compared to noninfected women (no-IPI group) according to the IPI species findings of a previous study [39]. Subgroup analyses for ABOs were conducted comparing noninfected women with *i*) monoparasitic-IPI, *ii*) polyparastic-IPI, *iii*) helminths, i*v*) *S. intercalatum*, and *v*) *Entamoeba histolytica*. A flowchart of participation in the study is shown in Figure 1.

Sample size determination and sampling procedures

The sample size for the initial study followed the WHO-steps approach, applying a web-based sample size calculator, Raosoft, and was supported by PASS software, which suggested a minimum sample size of S = 355 [47-49]. A total of 518 participants were initially enrolled based on the following assumptions: two-sided 95% confidence level, power of 80% to detect an odds ratio of at least 2 for adverse birth outcomes [39]. A power analysis was additionally performed, varying from 80% to 87% for outcomes such as having maternal anaemia [39].
Participants were selected through random sampling, from the pile of mothers′ medical admission folders [39]. Women were invited to participate in the study after admission but were interviewed only after they completely recovered from the baby′s delivery [39].

Data collection tools, procedures, and quality control

Data were collected by a pretested, structured interviewer-administered questionnaire developed from the Sao Tome & Principe Demographic and Health Survey (DHS) and similar studies [28,37]. Additionally, a standard abstraction checklist from ANC pregnancy cards and newborn records was conducted. The ANC pregnancy card was used to collect information from the participants, regarding copro-parasitological results, treatments, and haemoglobin levels. We also used secondary neonatal clinical data, which were prospectively abstracted from newborns' medical records, regarding low-birth-weight, prematurity, and stillbirth data.
The questionnaires were checked for completeness and consistency. Data collection was regularly reviewed by the supervisors. The principal investigator (a pediatrician) executed and was responsible for the field activities as follows: 1) obtaining consent and enrollment of the mothers, 2) data collection from ANC cards plus maternal and newborn records, 3) newborns' clinical exams (for diagnosis confirmation), 4) face-to-face interviews, and 5) entry of all data collection into the app survey tool. Finally, double data entry was performed to minimize errors during data entry.

Operational definition of variables

In this study, prematurity was defined as birth occurring at less than 37 weeks of gestation [50]. Gestational age at birth was calculated from the first day of the woman's last menstrual period and counted in

completed weeks [51,52]. Low-birth-weight was defined as an infant born with a weight of less than 2500 grams [51]. Stillbirth was defined, according to the WHO/ICD for International comparison and reporting, as a baby born without any signs of life at or after 28 weeks of gestation or at least 1000 g in birth weight [52]. Maternal anaemia was defined as a haemoglobin concentration <11 g/dl [53].

The exposure variables in this study included the parasites identified among the 361 copro-parasitological tests performed among pregnant women during ANC recorded in our previous study [39]. A total of 210 copro-parasitological tests were positive [39]. Helminthiasis or combined-group added to a total of 202 monoparasitic infections: 191 (90.9%) roundworm, 29 (13.8%) whipworm, 3 (1.4%) hookworm, 1 (0.5%) *Strongyloides stercoralis* [39]. *Schistosoma intercalatum* infection was found in 11 pregnant women and *Entamoeba histolytica* was found in 7 women [39]. Cases of polyparasitism, defined as the presence of two or more parasite species in the same host, were found in 25 (11.9%) pregnant women [39].

Data management and statistical analyses

Data were entered into the QuickTapSurvey (2010-2021 Formstack) offline app survey tool. Data entry for this study into the app survey was first cleaned by creating a data entry field in Excel, and all categorical responses were checked for completeness and accuracy and to eliminate errors and inconsistent data. Data were further analysed using the Statistical Package for the Social Sciences for Windows, version 25.0 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.).

Data analysis in this study was carried out in two stages. The first stage involved pooling data for descriptive statistics with categorical variables presented as frequencies and percentages and quantitative variables presented as the mean and standard deviation, as appropriate. For the ABO analysis, pregnant women with an IPI (n=210) were divided according to the presence of one or more parasites in the copro-parasitological test and the specific type of parasite. Subgroup analyses for ABOs were conducted comparing the no-IPI or noninfected women group (n=151) with *i*) monoparasitic-IPI (n=145), *ii*) polyparastic-IPI (n=25), *iii*) helminths (n=162), *iv*) *S. intercalatum* (n=11), and *v*) *Entamoeba histolytica*. (n=7). This second stage involved the use of the non-parametric chi-square test and Fisher's exact test, as appropriate. A level of significance of α=0.05 was considered.

Ethics approval and consent to participate

This study was approved by dedicated ethics oversight bodies, namely the Ministry of Health of Sao Tome & Principe and the main board of the Hospital Dr. Ayres de Menezes. The study complies with the Declaration of Helsinki. Written informed consent was obtained from all participants after the purpose of the research was explained orally by the researcher. Approval by the participants' parents or legal guardians was obtained in the case of adolescents under 16 years of age or for illiterate women.

Table 1: Sociodemographic, pregnancy-related and community-level characteristics of the participants
Abbreviations: ANC: antenatal care

Variables	Frequency (n=361)	Percentage (%)
Age		
14-19	65	18
20-34	233	64.5
≥35	63	17.5
Education		
none	12	3.3
primary	196	54.3
secondary	126	34.9
higher	27	7.5
Employment		
not working	250	69.6
working	109	30.4
Marital status		
union/married	303	85.4
single	52	14.6
Baby's father education		
none	8	3.3
primary	116	47.3
secondary	94	38.4
higher	27	11
Residence		
urban	166	46.4
rural	192	53.6
Water source		
improved water	304	84.2
no	57	15.8
Household sanitation		
with sanitation	202	56.4
open defecation	156	43.6
Parity		
0	103	28.5
1-4	227	62.9
5+	31	8.6
ANC visits		
< 4	24	6.6
4-7	168	46.5
≥ 8	169	46.8

Results

Characteristics of the study participants

Of the 361 pregnant women included, 233 (64.5%) were aged 20 to 34, and the mean age was 26.96 ±7.0 years (minimum age 14 and maximum 43 years). Three hundred and three (85.4%) participants were married, 196 (54.3%) ended school with a primary level of education, and 12 (3.3%) were illiterate. Unemployment was identified in 250 (69.6%) women. Table 1 shows the sociodemographic characteristics of the participants.

Pregnancy-related characteristics: A parity of one to four was observed in 227 (62.9%) pregnant women, with 103 (28.5%) of the participants being nulliparous and 31 (8.6%) grand multiparous. Complete ANC service utilization with ANC 8+ contacts was achieved by 169 (46.8%) pregnant women, while 24 (6.6%) had fewer than 4 ANC contacts.

Community-level feature: residency in a rural area was assessed for 192 (53.6%) participants. Access to improved water sources was reported for 304 (84.2%) pregnant women, and 156 (43.6%) practiced open defecation.

Adverse outcomes

Of the 361 participants, maternal anaemia was identified in 127 (39.6%) pregnant women. Child-related ABOs were found in 82 (23%) newborns, as follows: 26 (8.1%) premature, 48 (14.9%) low-birth-weight and 8 (2.5%) stillbirths (Table 2).

Table 2: Adverse outcomes observed among the participants (n=321)

Variables	Frequency (n=321)*	Percentage (%)
Maternal anaemia		
yes	127	39.6
no	194	60.4
Prematurity		
yes	26	8.1
no	295	91.9
Low-birth-weight		
yes	48	14.9
no	273	85.1
Stillbirth		
yes	8	2.5
no	313	97.5

*Forty women who received adequate anthelmintic treatment (albendazole, mebendazole or piperazine) for helminthic infection during pregnancy were excluded.

Abbreviations: IPI - intestinal parasitic infection

Association between ABOs and IPIs in pregnant women

ABOs were compared between pregnant women with monoparasitic-IPI (n=145) and noninfected women (n=151), as described in Table 3. Maternal anaemia was found in 46.7% and 38.7% of pregnant women in the monoparasitic-IPI and no-IPI groups, respectively. A statistically significant difference was not found between groups for maternal anaemia. Regarding offspring features, ABOs in the monoparasitic-IPI group compared to the no-IPI group, namely, prematurity (6.2% vs 10.9%), low-birth-weight (11% vs 19.2%) and stillbirths (3.4% vs 1.3%), had no statistically significant difference.

Table 3: Adverse outcomes in pregnant women with a monoparasitic-IPI compared to the noninfected group

	monoparasitic- IPI (n=145) n (%)	no-IPI (n=151) n (%)	*p* value
Maternal anaemia			0.182
yes	63 (46.7)	55 (38.7)	
no	72 (53.3)	87 (61.3)	
Prematurity			0.175
yes	9 (6.2)	16 (10.6)	
no	136 (93.8)	135 (89.4)	
Low-birth-weight			0.070*
yes	16 (11)	29 (19.2)	
no	129 (89)	122 (80.8)	
Stillbirth			0.275*
yes	5 (3.4)	2 (1.3)	
no	140 (96.6)	149 (49)	

*Fisher's exact test

Abbreviations: IPI - intestinal parasitic infection

ABOs between pregnant women with polyparasitic-IPI (n=25) and noninfected pregnant women (n=151), described in Table 4, also had no statistically significant difference.

Table 4: Adverse outcomes in pregnant women with a polyparasitic-IPI compared to the noninfected group

	Polyparasitic-IPI (n=25) n (%)	no-IPI (n=151) n (%)	*p* value
Maternal anaemia			0.796
yes	9 (36)	55 (38.7)	
no	16 (64)	87 (61.3)	
Prematurity			0.473*
yes	1 (4)	16 (10.6)	
no	24 (96)	135 (89.4)	
Low-birth-weight			0.576*
yes	3 (12)	29 (19.2)	
no	22 (88)	122 (80.8)	
Stillbirth			0.370*
yes	1 (4)	2 (1.3)	
no	24 (96)	149 (49)	

*Fisher's exact test

Abbreviations: IPI - intestinal parasitic infection

Soil-Transmitted Helminths

The 162 untreated pregnant women with a helminthic infection had the following ABOs: 45.8% maternal anaemia, 6.2% prematurity, 11.7% low-birth-weight and 3.7% stillbirth rate (Table 5). No statistically significant difference was found for ABOs between women infected with helminthic infection and noninfected women. The low-birth-weight comparison between the helminth subgroup (11.7%) and the noninfected group (19.2%) had a p value=0.067.

Table 5: Adverse outcomes in pregnant women with a helminthic infection compared to the noninfected group

	Helminths[1] (n=162) n (%)	no-IPI (n=151) n (%)	*p* value
Maternal anaemia			0.223
yes	70 (45.8)	55 (38.7)	
no	83 (54.2)	87 (61.3)	
Prematurity			0.157
yes	10 (6.2)	16 (10.6)	
no	152 (93.8)	135 (89.4)	
Low-birth-weight			0.067
yes	19 (11.7)	29 (19.2)	
no	143 (88.3)	122 (80.8)	
Stillbirth			0.285*
yes	6 (3.7)	2 (1.3)	
no	156 (96.3)	149 (98.7)	

*Fisher´s exact test

[1]For helminth-related adverse outcomes, 40 women who received adequate anthelmintic treatment (albendazole, mebendazole or piperazine) during pregnancy were excluded from this ABO analysis.

Abbreviations: IPI - intestinal parasitic infection

Schistosoma intercalatum

Out of the eleven pregnant women with a *S. intercalatum*-positive copro-parasitological test, one low-birth-weight baby was identified, and no preterm baby or stillbirth outcomes were found (Table 6). Maternal anaemia was found in 36.4% and 38.7% of pregnant women with a *S. intercalatum*-IPI and noninfected women, respectively.

No statistically significant difference was found for low-birth-weight and maternal anaemia between the two groups.

Table 6: Adverse outcomes in pregnant women with a *S. intercalatum* positive copro-parasitological result compared to the noninfected group

	S. intercalatum (n=11) n (%)	no-IPI (n=151) n (%)	*p* value
Maternal anaemia			1.000*
yes	4 (36.4)	55 (38.7)	
no	7 (63.6)	87 (61.3)	
Prematurity			0.603*
yes	0	16 (10.6)	
no	11 (100)	135 (89.4)	
Low-birth-weight			0.691*
yes	1 (9.1)	29 (19.2)	
no	10 (90.9)	122 (80.8)	
Stillbirth			1.000*
yes	0	2 (1.3)	
no	11 (100)	149 (98.7)	

*Fisher´s exact test

Abbreviations: IPI - intestinal parasitic infection

Entamoeba histolytica

All seven pregnant women with an *Entamoeba histolytica*-positive copro-parasitological test had no preterm baby, low-birth-weight or stillborn offspring (Table 7). Maternal anaemia was found in 16.7% and 38.7% of women with *Entamoeba histolytica*-IPI and noninfected women, respectively. No statistically significant difference was found for maternal anaemia between women with *Entamoeba histolytica* and noninfected women.

Table 7: Adverse outcomes in pregnant women with an Entamoeba histolytica-positive copro-parasitological result compared to the noninfected group

	E histolytica (n=7) n (%)	no-IPI (n=151) n (%)	*p* value
Maternal anaemia			0.409*
yes	1 (16.7)	55 (38.7)	
no	5 (83.3)	87 (61.3)	
Prematurity			1.000*
yes	0	16 (10.6)	
no	7 (100)	135 (89.4)	
Low-birth-weight			0.351*
yes	0	29 (19.2)	
no	7 (100)	122 (80.8)	
Stillbirth			1.000*
yes	0	2 (1.3)	
no	7 (100)	149 (98.7)	

*Fisher´s exact test

Abbreviations: IPI - intestinal parasitic infection

Discussion

Women living in endemic countries are known to have a higher risk of acquiring an IPI during their pregnancy and consequently to suffer eventual complications from these NTDs [2,9-14]. Thus, this study was conducted to clarify the adverse outcomes among these IPI-infected pregnant women and their offspring in Sao Tome & Principe.

Overall, approximately 40% of women in this study were anaemic, similar to the prevalence of 46% anaemia among pregnant women in SSA countries and lower than the 61% rate published for the country [46,53]. Confounders for adverse outcomes, namely HIV infection, sickle cell disorder, and malaria were excluded from this analysis. Nonetheless, although IPIs are reported to cause or aggravate maternal anaemia through multiple mechanisms, a statistically significant difference was not found when each infected subgroup was compared to the noninfected counterpart, highlighting that anaemia in this setting is mainly multifactorial [5].

Approximately one-quarter of the newborns had child-related adverse outcomes, mostly due to low-birth-weight. When child-related ABOs were compared between IPI subgroups and their noninfected

counterparts, no statistically significant difference was found between the groups. However, it should be acknowledged that an almost significant statistically significant difference (p value=0.067) was found, suggesting that pregnant women with a helminthic infection had fewer low-birth-weight babies than noninfected mothers. This is in accordance with some studies of helminths alone that have found no association between infection and birthweight [16,54-55]. Fairley et al. found that pregnant women with helminthic infections have higher birth weights even in the presence of coinfections [55]. Thus, it can be speculated that helminthic infection can promote an immunological environment surrounding the uterus into a more advantageous milieu, which can contribute to enhanced foetal weight gain, although more studies are needed to clarify this [6].

In our study, factors such as the parasitic infection intensity and the timing of infection (before pregnancy or in which trimester), were not available, missing out on major clues that could explain or support our findings [18,56-58]. However, the main factor supporting our findings is the type of parasite infecting the participants of this study and its respective pathogenesis mechanisms [1]. As previously mentioned, the most predominant parasite in this study was the roundworm *A. lumbricoides* (90.9%), which is known to be mainly an asymptomatic infection [2,39]. This lack of association between *A. lumbricoides* infection and adverse outcomes, such as maternal anaemia, prematurity and stillbirths, was also reported in other studies conducted in SSA countries, namely, in Kenya and in Tanzania [9,10]. In contrast, Rodríguez-Morales et al. in Venezuela reported that *A. lumbricoides* infection represented a twofold risk for anaemia at pregnancy, similar to Demeke G et al. found in Ethiopia [14,57].

Regarding schistosomiasis during pregnancy, as previously mentioned, there is a paucity of studies. To the best of our knowledge, this is the first report on *S. intercalatum* during pregnancy [39]. Of the eleven pregnant women with a positive *S. intercalatum* copro-parasitological test, only four women had maternal anaemia, and one newborn had low-birth-weight. The lack of adverse outcomes with this parasite can rely on the fact that *S. intercalatum* infections are known to be asymptomatic or to be associated with a dysenteric syndrome with bloody stools without further complications [24,25,45,59]. Moreover, intestinal schistosomiasis due to *S. intercalatum* is typically characterized by a low location of the lesions at the level of the rectum and sigmoid colon and relatively minor liver pathology without portal hypertension [24,25,59]. The current national preventive chemotherapy programme with praziquantel for schistosomiasis control only targets school children, missing out on other at-risk populations [35,39]. Therefore, our findings also have some policy implications since the 2017 Sao Tome & Principe national survey suggested the elimination of *S. intercalatum* among children, claiming to be one of the first countries to eliminate schistosomiasis [35]. Thus, according to our research, *S. intercalatum* is still a reality among pregnant women in the country; thus, women-of-reproductive age should be included in the country's preventive chemotherapy programmes to achieve the goal of eliminating schistosomiasis in the country [23].

Entamoeba histolytica is a rare NTD, and none of our seven pregnant women enrolled with a copro-parasitological test positive for *Entamoeba histolytica* had any child-related adverse outcomes, and only one mother had anaemia. This finding is contrary to the Mahande study, which reported twofold increased odds of preterm delivery among women with *Entamoeba* infection compared with noninfected women, probably due to penetration of the intestinal mucosa and placental barrier by *E. histolytica* [10]. Amebiasis is reported to be more severe in pregnant women than in non-pregnant women, linked to the reduced production of IgA during pregnancy, which may lead to subchronic inflammation and placental dysfunction resulting in preeclampsia, preterm delivery, and foetal growth restriction [29,30]. None of the drugs used in the country for preventive chemotherapy programmes have efficacy in treating *Entamoeba* infections [30,35]. Thus, routine ANC screening for IPIs through copro-parasitological exams should be maintained, and pregnant women should receive adequate follow-up [30,39].

It would also be relevant to introduce the possibility that the amoebae identified as *E. histolytica* may, in fact, be *E. dispar* or *E. moshkovskii*—morphologically identical but non-pathogenic species [29,30]. This could explain the absence of any clinical manifestations associated with the infection.

Overall, this study is a useful starting point that can assist Sao Tome & Principe policy makers in understanding the impact of IPIs among pregnant women and in rethinking the targets for preventive chemotherapy programmes, including women-of-reproductive age, as previously mentioned for schistosomiasis.

Nonetheless, primarily, what this study brings, is

the opportunity to discuss what are the real benefits and risks of providing anthelmintic treatment during pregnancy for this specific setting, facing the lack of adverse outcomes associated with roundworms infections.

As recently highlighted by some authors, there may be unexpected consequences of IPI treatment, as maternal infections can affect the priming of infant immune systems, with potential effects on children later in life [16,22]. Additionally, questions remain regarding the efficacy of anthelmintic treatment reported in some studies [16,22]. For instance, efficacy can be linked to cases with very high parasite burdens, dietary insufficiencies or both and that pregnant women adequately nourished, without comorbidities and with moderate or low parasite burden, may not benefit from anthelmintic treatment [16,22]. On the other hand, anthelmintic treatment during pregnancy has been associated with an increased incidence of eczema in children, suggesting that anthelmintics may affect the development of mechanisms regulating child immune responses [7,16,60]. In addition, anthelmintic treatment may also have additional risks by altering maternal blood glucose regulation, microbiota, or hormonal environment [16]. Therefore, some caution to promote broad efforts to treat all pregnant women during pregnancy is warranted until future studies clarify the real impact and outcomes and how they play out under different ecological conditions [16].

Therefore, treating infected pregnant women is far from straightforward, and the debate is whether helminthic infections are "old enemies or old friends", especially during pregnancy [16,22].

Recent studies focused on the benefits of helminthic infections. Some authors argue that immune regulation by parasites, mainly the host immune response to roundworms, can increase fertility rates in infected women [6]. Moreover, in endemic countries, mainly for *Ascaris lumbricoides* or roundworms, the burden of infection has been associated with lower frequencies of allergic symptoms and skin test positivity [6].

Therefore, if in our previously published study, we recommended that all the "treatment missing opportunities" identified among pregnant women with an IPI in Sao Tome & Principe be urgently addressed, we now consider that there are more benefits in postponing anthelmintic treatment in all asymptomatic and healthy pregnant women with a helminthic infection after the baby's delivery [39].

Strengths and limitations

This cross-sectional study addresses an understudied population and, notably, is the first to report on *Schistosoma intercalatum* infections during pregnancy and their associated outcomes. A robust approach was used to control for confounding factors, as participants with HIV infection, sickle cell disorder, and malaria were excluded, allowing for a clearer assessment of the effects of intestinal parasitic infections. Importantly, the study yields policy-relevant findings by highlighting gaps in national deworming programs and emphasizing the need to extend preventive measures to women beyond school-aged children.

An important limitation is the negligible number of participants with *S. intercalatum* and *Entamoeba histolytica* found in the study. Additionally, the amoebae identified in this study as *E. histolytica* may, in fact, be *E. dispar* or *E. moshkovskii*—morphologically identical but non-pathogenic species.

On the other hand, maternal factors such as gestational weight gain and BMI were not analyzed in this study, as these measurements are not performed during ANC contacts in the country, missing a key mediator. Thus, future studies with larger samples will be needed to clarify the lack of adverse outcomes associated with these species. Other limitations, commented before, were that information regarding the intensity and timing of the parasitic infection was not available. Notwithstanding these limitations, this study represents a significant first step in the description of IPIs and ABOs and key modifiable associated factors in this resource-constrained setting.

Future studies

Longitudinal cohort studies to assess infection timing (e.g., trimester-specific effects) and intensity on maternal-fetal outcome are needed to better understand these host–parasite interactions and the overall impact and role of intestinal parasites among pregnant women and their offspring. Additionally, Immunological research on how helminthic infections modulate maternal-foetal immune responses and infant health trajectories are very important, since helminthic infections are known to affect blood glucose, insulin resistance and diabetes, linking it to improvement of glucose tolerance and lower blood levels, it should be important to include the association with gestational diabetes and IPI in future studies [16]. Preeclampsia associations with intestinal

parasites should also be included in future studies, since immunological effects of helminths on maternal immunity, by increasing maternal tolerance of the foetus and by moderating inflammatory responses, are believed to have a protective role from preeclampsia [16].

Conclusions

This study provides important insights into intestinal parasitic infections (IPIs) among pregnant women in Sao Tome & Príncipe and highlights critical gaps in current public health strategies. No significant adverse outcomes were observed in association with helminthic infections during pregnancy; in fact, the rate of low-birth-weight was marginally lower among infected mothers compared to their uninfected counterparts. Notably, roundworms (*Ascaris lumbricoides*) were the predominant species identified in this cohort, which may explain the absence of complications in both pregnant women and their offspring.

Furthermore, the findings suggest that claims regarding the elimination of schistosomiasis in STP may be premature. *Schistosoma intercalatum* infections persist among pregnant women, indicating a need to expand preventive chemotherapy programs to include women of reproductive age.

However, the administration of anthelmintic treatment during pregnancy should be approached with caution. Emerging evidence suggests that asymptomatic helminthic infections may confer immunological benefits to offspring, and treatment could potentially disrupt the maternal microbiota or increase the risk of childhood eczema.

In summary, while the study supports the safety of deferring anthelmintic treatment in asymptomatic, healthy pregnant women with helminthic infections until after delivery, it also underscores the necessity of revising public health policies to address persistent parasitic infections in this population.

Declarations

Ethics approval and consent to participate

This study was approved by dedicated ethics oversight bodies, namely the Ministry of Health of Sao Tome & Principe and the main board of the Hospital Dr. Ayres de Menezes. The study complies with the Declaration of Helsinki. Written informed consent was obtained from all participants after the purpose of the research was explained orally by the researcher. Approval by the participants′ parents or legal guardians was obtained in the case of adolescents under 16 years of age or for illiterate women.

Availability of data and materials

All data generated or analysed during this study are included in this paper or in the published article.[39]

Competing interests

The authors declare that they have no financial or nofinancial competing interests.

Consent for publication

Not applicable.

Authors' contributions

AV, MCM, and FP performed the conception and design of the study. AV was responsible for field activities, data collection, and writing the manuscript. MCM and FP critically evaluated and made progressive suggestions throughout the study and revised the manuscript. MA and ALP performed the statistical analysis and reviewed the manuscript. SS and NB were involved in the study design at the country level. All the authors read and approved the final draft of the manuscript.

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Abbreviations

HAM: Hospital Dr. Ayres de Menezes; ANC: antenatal care; WHO: World Health Organization; NTD: Neglected Tropical Diseases.

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Bibliography

1. Mohan S, Halle-Ekane G, Konje JC. Intestinal parasitic infections in pregnancy-A review. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2020;254:59–63.

2. Yakasai I, Umar U. A review of parasitic infestation in pregnancy. Asian Journal of Natural and Applied Sciences. 2013;2(1):31–8.

3. Kaiser RWJ, Allgeier J, Philipp AB, Mayerle J, Rothe C, Wallrauch C, et al. Development of amoebic liver abscess in early pregnancy years after initial amoebic exposure: a case report. BMC Gastroenterol [Internet]. 2020;20(1). Available from: http://dx.doi.org/10.1186/s12876-020-01567-7

4. Roberts T, Gravett CA, Velu PP. Epidemiology and aetiology of maternal parasitic infections in low-and middle-income countries. Journal of global health. 2011;1(2).

5. McClure EM, Meshnick SR, Mungai P, Malhotra I, King CL, Goldenberg RL, et al. The association of parasitic infections in pregnancy and maternal and fetal anemia: A cohort study in coastal Kenya. PLoS Negl Trop Dis [Internet]. 2014;8(2):e2724. Available from: http://dx.doi.org/10.1371/journal.pntd.0002724

6. Persson G, Ekmann JR, Hviid TVF. Reflections upon immunological mechanisms involved in fertility, pregnancy and parasite infections. J Reprod Immunol [Internet]. 2019;136(102610):102610. Available from: http://dx.doi.org/10.1016/j.jri.2019.08.001

7. Elliott AM, Mpairwe H, Quigley MA, Nampijja M, Muhangi L, Oweka-Onyee J, et al. Helminth infection during pregnancy and development of infantile eczema. JAMA [Internet]. 2005;294(16):2032–4. Available from: http://dx.doi.org/10.1001/jama.294.16.2032-c

8. Dewals BG, Layland LE, Prazeres da Costa C, Horsnell WG. Maternal helminth infections and the shaping of offspring immunity. Parasite Immunol [Internet]. 2019;41(3). Available from: http://dx.doi.org/10.1111/pim.12599

9. Wekesa AW, Mulambalah CS, Muleke CI, Odhiambo R. Intestinal helminth infections in pregnant women attending antenatal clinic at kitale district hospital, Kenya. J Parasitol Res [Internet]. 2014;2014:1–5. Available from: http://dx.doi.org/10.1155/2014/823923

10. Mahande AM, Mahande MJ. Prevalence of parasitic infections and associations with pregnancy complications and outcomes in northern Tanzania: a registry-based cross-sectional study. BMC Infect Dis [Internet]. 2016;16(1). Available from: http://dx.doi.org/10.1186/s12879-016-1413-6

11. Jourdan PM, Lamberton PHL, Fenwick A, Addiss DG. Soil-transmitted helminth infections. Lancet [Internet]. 2018;391(10117):252–65. Available from: http://dx.doi.org/10.1016/s0140-6736(17)31930-x

12. Elliott AM, Ndibazza J, Mpairwe H, Muhangi L, Webb EL, Kizito D, et al. Treatment with anthelminthics during pregnancy: what gains and what risks for the mother and child? Parasitology [Internet]. 2011;138(12):1499–507. Available from: http://dx.doi.org/10.1017/s0031182011001053

13. Feleke BE, Jember TH. Prevalence of helminthic infections and determinant factors among pregnant women in Mecha district, Northwest Ethiopia: a cross sectional study. BMC Infect Dis [Internet]. 2018;18(1). Available from: http://dx.doi.org/10.1186/s12879-018-3291-

14. Rodríguez-Morales AJ, Barbella RA, Case C, Arria M, Ravelo M, Perez H, et al. Intestinal parasitic infections among pregnant women in Venezuela. Infect Dis Obstet Gynecol [Internet]. 2006;2006:1–5. Available from: http://dx.doi.org/10.1155/idog/2006/23125

15. Gyorkos TW, Larocque R, Casapia M, Gotuzzo E. Lack of risk of adverse birth outcomes after deworming in pregnant women. Pediatr Infect Dis J [Internet]. 2006;25(9):791–4. Available from: http://dx.doi.org/10.1097/01.inf.0000234068.25760.97

16. Blackwell AD. Helminth infection during pregnancy: insights from evolutionary ecology. Int J Womens Health [Internet]. 2016;8:651–61. Available from: http://dx.doi.org/10.2147/ijwh.s103529

17. Stratton JA, Miller RD, Schmidt P. Effect of maternal parasitic disease on the neonate. Am J Reprod Immunol Microbiol [Internet]. 1985;8(4):141–2. Available from: http://dx.doi.org/10.1111/j.1600-0897.1985.tb00327.x

18. Heaton J, Shippey S, Macri C, Macedonia C. Intestinal helminthes infestation in pregnancy: a case report and literature review. Mil Med. 2002;167(11):954–5.

19. Bolka A, Gebremedhin S. Prevalence of intestinal parasitic infection and its association with anemia among pregnant women in Wondo Genet district, Southern Ethiopia: a cross-sectional study. BMC Infect Dis [Internet]. 2019;19(1). Available from: http://dx.doi.org/10.1186/s12879-019-4135-8

20. Bangert M, Bancalari P, Mupfasoni D, Mikhailov A, Gabrielli AF, Montresor A. Provision of deworming intervention to pregnant women by antenatal services in countries endemic for soil-transmitted helminthiasis. PLoS Negl Trop Dis [Internet]. 2019;13(5):e0007406. Available from: http://dx.doi.org/10.1371/journal.pntd.0007406

21. Ajanga A, Lwambo NJS, Blair L, Nyandindi U, Fenwick A, Brooker S. Schistosoma mansoni in pregnancy and associations with anaemia in northwest Tanzania. Trans R Soc Trop Med Hyg [Internet]. 2006;100(1):59–63. Available from: http://dx.doi.org/10.1016/j.trstmh.2005.06.024

22. Salam RA, Haider BA, Humayun Q, Bhutta ZA. Effect of administration of antihelminthics for soil-transmitted helminths during pregnancy. Cochrane Libr [Internet]. 2015; Available from: http://dx.doi.org/10.1002/14651858.cd005547.pub3

23. World Health Organization guideline on control and elimination of human schistosomiasis. Geneva: World Health Organization. 2022 [Internet]. WHO. [cited 2023 Jan 5]. Available from: https://www.who.int/publications/i/item/97892 40041608

24. Tzanetou K, Astriti M, Delis V, Moustakas G, Choreftaki T, Papaliodi E, et al. Intestinal schistosomiasis caused by both Schistosoma intercalatum and Schistosoma mansoni. Travel Med Infect Dis [Internet]. 2010;8(3):184–9. Available from: http://dx.doi.org/10.1016/j.tmaid.2010.04.003

25. Tchuenté LA, Southgate VR, Jourdane J. Schistosoma intercalatum: an endangered species in Cameroon? Trends in parasitology. 2003;19(9):389–93

26. Marchese V, Beltrame A, Angheben A, Monteiro GB, Giorli G, Perandin F, et al. Schistosomiasis in immigrants, refugees and travellers in an Italian referral centre for tropical diseases. Infect Dis Poverty [Internet]. 2018;7(1). Available from: http://dx.doi.org/10.1186/s40249-018-0440-5

27. Friedman JF, Mital P, Kanzaria HK, Olds GR, Kurtis JD. Schistosomiasis and pregnancy. Trends in parasitology. 2007;23:159–64.

28. Walana W, Crowther S, Tay K. Prevalence of intestinal protozoan infestation among primary school children in Urban and peri-urban communities in Kumasi. Ghana. 2014;2(2):52–7.

29. Nhidza AF, Naicker T, Stray-Pedersen B, Chisango TJ, Sibanda EP, Ismail A, et al. Immune response to asymptomatic infections by Entamoeba histolytica and other enteric pathogens in pregnant women and their infants in a high HIV burdened setting in Zimbabwe. J Microbiol Immunol Infect [Internet]. 2020;53(4):612–21. Available from: http://dx.doi.org/10.1016/j.jmii.2018.11.005

30. Kantor M, Abrantes A, Estevez A, Schiller A, Torrent J, Gascon J, et al. Entamoeba histolytica: Updates in clinical manifestation, pathogenesis, and vaccine development. Can J Gastroenterol Hepatol [Internet]. 2018;2018:1–6. Available from: http://dx.doi.org/10.1155/2018/4601420

31. Brooker S, Hotez PJ, Bundy DAP. Hookworm-related anaemia among pregnant women: A systematic review. PLoS Negl Trop Dis [Internet]. 2008;2(9):e291. Available from: http://dx.doi.org/10.1371/journal.pntd.0000291

32. World Health Organisation Deworming: Every Girl and Every Woman has the Right to be Treated. 2018 [Internet]. WHO. [cited 2023 Apr 4]. Available from: https://www.who.int/neglected_diseases/news

33. Bundy DAP, Chan MS, Savioli L. Hookworm infection in pregnancy. Trans R Soc Trop Med Hyg [Internet]. 1995;89(5):521–2. Available from: http://dx.doi.org/10.1016/0035-9203(95)90093-4

34. Sao Tome and Principe WHO statistical profile [Internet]. WHO. [cited 2023 Jan 1]. Available from: https://www.who.int/gho/countries/stp.pdf.

35. Byrne A, Rosário A, da Conceição Ferreira M, de Jesus Trovoada dos Santos M, Rollinson D, Vaz Nery S. Progress towards control and elimination of neglected tropical diseases targeted by preventive chemotherapy in São Tomé e Príncipe. Trans R Soc Trop Med Hyg [Internet]. 2022;116(5):446–53. Available from: http://dx.doi.org/10.1093/trstmh/trab153

36. Garzón M, Pereira-da-Silva L, Seixas J, Papoila AL, Alves M, Ferreira F, et al. Association of enteric parasitic infections with intestinal inflammation and permeability in asymptomatic infants of São Tomé Island. Pathog Glob Health [Internet]. 2017;111(3):116–27. Available from: http://dx.doi.org/10.1080/20477724.2017.1299831

37. Belo S, Rompão H, Gonçalves L, Grácio MAA. Prevalence, behavioural and social factors associated with Schistosoma intercalatum and geohelminth infections in São Tomé and Principe. Parassitologia. 2005;47(2):227–31.

38. Ferreira FS, Baptista-Fernandes T, Oliveira D, Rodrigues R, Neves E, Lima A, et al. Giardia duodenalis and Soil-transmitted Helminths infections in Children in Sao Tome and Principe: Do we think Giardia when addressing Parasite Control? J Trop Pediatr [Internet]. 2015;61(2):106–12. Available from: http://dx.doi.org/10.1093/tropej/fmu078

39. Vasconcelos A, Sousa S, Bandeira N, Alves M, Papoila AL, Pereira F, et al. Intestinal parasitic infections, treatment and associated factors among pregnant women in Sao Tome and Principe: A cross-sectional study. J Trop Med [Internet]. 2022;2022:1–11. Available from: http://dx.doi.org/10.1155/2022/7492020

40. Vasconcelos A, Bandeira N, Sousa S, Machado MC, Pereira F. Adolescent pregnancy in Sao Tome and Principe: are there different obstetric and perinatal outcomes? BMC Pregnancy Childbirth [Internet]. 2022;22(1). Available from: http://dx.doi.org/10.1186/s12884-022-04779-9

41. Vasconcelos A, Bandeira N, Sousa S, Pereira F, Machado M do C. Adolescent pregnancy in Sao Tome and Principe: a cross-sectional hospital-based study. BMC Pregnancy Childbirth [Internet]. 2022;22(1). Available from: http://dx.doi.org/10.1186/s12884-022-04632-z

42. Vasconcelos A, Sousa S, Bandeira N, Alves M, Papoila AL, Pereira F, et al. Antenatal screenings and maternal diagnosis among pregnant women in Sao Tome & Principe—Missed opportunities to improve neonatal health: A hospital-based study. PLOS Glob Public Health [Internet]. 2022;2(12):e0001444. Available from: http://dx.doi.org/10.1371/journal.pgph.0001444

43. Vasconcelos A, Sousa S, Bandeira N, Alves M, Papoila AL, Pereira F, et al. Adverse birth outcomes and associated factors among newborns delivered in Sao Tome & Principe: A case-control study. PLoS One [Internet]. 2023;18(7):e0276348. Available from: http://dx.doi.org/10.1371/journal.pone.0276348

44. Vasconcelos A, Sousa S, Bandeira N, Alves M, Papoila AL, Pereira F, et al. Determinants of antenatal care utilization – contacts and screenings – in Sao Tome & Principe: a hospital-based cross-sectional study. Arch Public Health [Internet]. 2023;81(1). Available from: http://dx.doi.org/10.1186/s13690-023-01123-1

45. Gendrel D, Kombila M, Beaudoin-Leblevec G, Richard-Lenoble D. Nontyphoidal Salmonellal Septicemia in Gabonese Children Infected with Schistosoma intercalatum. Clin Infect Dis [Internet]. 1994;18(1):103–5. Available from: http://dx.doi.org/10.1093/clinids/18.1.103

46. Estratégia integrada de Saúde Reprodutiva, Materna, Neonatal, Infantil e do Adolescente e Nutrição 2019-2023 [Internet]. UNFPA São Tomé e Príncipe. 2021 [cited 2023 Dec 3]. Available from: https://saotomeandprincipe.unfpa.org/pt/publications/estrat%C3%A9gia-integrada-de-sa%C3%BAde-reprodutiva-materna-neonatal-infantil-e-do-adolescente-e

47. Lachenbruch PA, Lwanga SK, Lemeshow S. Sample size determination in health studies: A practical manual. J Am Stat Assoc [Internet]. 1991;86(416):1149. Available from: http://dx.doi.org/10.2307/2290547

48. Sample size calculator by raosoft, inc [Internet]. Raosoft.com. [cited 2023 Dec 3]. Available from: http://www.raosoft.com/samplesize.html

49. Ted Rosenberg MDMF, Buncher D. Sample size software [Internet]. Ncss.com. 2012 [cited 2023 Dec 3]. Available from: https://www.ncss.com/software/pass/

50. Mandy GT. Preterm birth: Definitions of prematurity, epidemiology, and risk factors for infant mortality [Internet]. Uptodate.com. [cited 2023 May 23].

51. Tchamo ME, Prista A, Leandro CG. Low birth weight, very low birth weight and extremely low birth weight in African children aged between 0 and 5 years old: a systematic review. J Dev Orig Health Dis [Internet]. 2016;7(4):408–15. Available from: http://dx.doi.org/10.1017/s2040174416000131

52. Tavares Da Silva F, Gonik B, McMillan M, Keech C, Dellicour S, Bhange S, et al. Stillbirth: Case definition and guidelines for data collection, analysis, and presentation of maternal immunization safety data. Vaccine [Internet]. 2016;34(49):6057–68. Available from: http://dx.doi.org/10.1016/j.vaccine.2016.03.044

53. Prevalence of anemia among pregnant women (%) - Sub-Saharan Africa [Internet]. World Bank Open Data. [cited 2023 Dec 3]. Available from: https://data.worldbank.org/indicator/SH.PRG.ANEM?locations=ZG

54. Ndibazza J, Muhangi L, Akishule D, Kiggundu M, Ameke C, Oweka J, et al. Effects of deworming during pregnancy on maternal and perinatal outcomes in Entebbe, Uganda: a randomized controlled trial. Clin Infect Dis [Internet]. 2010;50(4):531–40. Available from: http://dx.doi.org/10.1086/649924

55. Fairley JK, Kitron U, Mungai P, Malhotra I, Bisanzio D, King CH, et al. Birthweight in offspring of mothers with high prevalence of helminth and malaria infection in coastal Kenya. Am J Trop Med Hyg [Internet]. 2013;88(1):48–53. Available from: http://dx.doi.org/10.4269/ajtmh.2012.12-0371

56. Zegeye B, Keetile M, Ahinkorah BO, Ameyaw EK, Seidu A-A, Yaya S. Utilization of deworming medication and its associated factors among pregnant married women in 26 sub-Saharan African countries: a multi-country analysis. Trop Med Health [Internet]. 2021;49(1). Available from: http://dx.doi.org/10.1186/s41182-021-00343-x

57. Demeke G, Mengistu G, Abebaw A, Toru M, Yigzaw M, Shiferaw A, et al. Effects of intestinal parasite infection on hematological profiles of pregnant women attending antenatal care at Debre Markos Referral Hospital, Northwest Ethiopia: Institution based prospective cohort study. PLoS One [Internet]. 2021;16(5):e0250990. Available from: http://dx.doi.org/10.1371/journal.pone.0250990

58. Ahenkorah B, Nsiah K, Baffoe P, Ofosu W, Gyasi C, Owiredu E-W. Parasitic infections among pregnant women at first antenatal care visit in northern Ghana: A study of prevalence and associated factors. PLoS One [Internet]. 2020;15(7):e0236514. Available from: http://dx.doi.org/10.1371/journal.pone.0236514

59. Chu T, Liao C, Huang Y, Chang Y, Costa A, Ji D, et al. Prevalence of Schistosoma intercalatum and S. haematobium infection among primary schoolchildren in capital areas of Democratic Republic of São Tomé and Príncipe, west Africa. Iran J Parasitol. 2012;7(1):67–72

60. Ndibazza J, Mpairwe H, Webb EL, Mawa PA, Nampijja M, Muhangi L, et al. Impact of anthelminthic treatment in pregnancy and childhood on immunisations, infections and eczema in childhood: A randomised controlled trial. PLoS One [Internet]. 2012;7(12):e50325. Available from: http://dx.doi.org/10.1371/journal.pone.0050325