RESEARCH ARTICLE

Schistosoma, other helminth infections, and associated risk factors in preschool-aged children in urban Tanzania

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Abstract

Background

Despite the high prevalence of helminth infections among preschool-aged children, control programs in sub-Saharan countries primarily focus on school-aged populations. We assessed the prevalence of helminth infections and determined risk factors for infection among preschool-aged children in the urban setting of Dar es Salaam, Tanzania.

Methodology

Starting in October 2015, we conducted a 12-month prospective study among tuberculosis (TB)-exposed children under the age of 5 years and unexposed controls from neighboring households. At the time of recruitment, we collected medical histories, assessed development and cognitive functions, and performed medical examinations. We performed full blood cell counts and screened for HIV and malaria. Point-of-care circulating cathodic antigen (POC-CCA), urine filtration, Kato-Katz, FLOTAC, and Baermann tests were employed to detect helminth infections in urine and stool. Helminth infections were stratified for *Schistosoma* and other helminths to identify risk factors, using logistic regression.

Principal findings

We included 310 children with a median age of 26 months (inter quartile range 17–42 months) in the study. Among these, 189 were TB-exposed and 121 TB-unexposed. Two thirds of the children were anemic (hemoglobin level <11 g/dl) and the HIV prevalence was 1.3%. *Schistosoma* spp. was the predominant helminth species (15.8%; 95% confidence interval [CI] 12.1–20.3%). Other helminth infections were less frequent (9.0%, 95% CI 6.3–12.8%). Poor hygiene, use of household water sources, and TB-exposure were not associated with helminth infection. Development and cognitive scores did not significantly differ in

helminth-infected and uninfected peers, but hemoglobin levels were significantly lower in helminth-infected children (10.1 g/dl *vs.* 10.4 g/dl, p = 0.027).

Conclusions/significance

In Dar es Salaam, a city with more than 4 million inhabitants, the prevalence of *Schistosoma* spp. infection among preschool-aged children was unexpectedly high. Setting-specific interventions that target preschool-aged children and urban settlements should be considered to reduce the transmission of *Schistosoma* and other helminth infections and to improve children's health.

Author summary

In many African countries, children under the age of 5 years are at considerable risk of acquiring parasitic worm infections. Yet, most of the neglected tropical disease control programs in Africa do not include preschool-aged children in deworming campaigns. Chronic parasitic worm infections may impair children's growth and their cognitive development. We conducted a 12-month prospective study of children younger than 5 years in the Temeke district, Dar es Salaam—the economic capital of Tanzania—to assess the prevalence of parasitic worm infections. Among 310 included children, we found that one in six children was infected with the blood fluke *Schistosoma*, while one in 11 children were infected with soil-transmitted helminths. Anemia was found among 65% of children, particularly among those infected with parasitic worms. The high prevalence of *Schistosoma* infection in this urban setting, despite improved water supply and sanitation as well as limited open freshwater contact shows the pressing need to identify parasitic worm transmission hotspots in urban areas. Setting-specific interventions targeting preschool-aged children and urban settlements, among others, should be considered to reduce the transmission of *Schistosoma* and other parasitic worm infections.

Introduction

Helminth infections affect more than 1.5 billion people globally and are particularly common amongst economically deprived populations [1, 2]. The burden of helminthiases is high in settings with inadequate sanitation, overcrowding, and low socioeconomic status; the same characteristics that govern transmission of tuberculosis (TB) [3–7]. Helminth infections, though rarely fatal, cause considerable morbidity [8, 9]. In children, heavy intensity helminth infections can impair physical growth and cognitive development, and lead to micronutrient deficiencies and anemia [3, 10]. Subsequently, if anemia and its underlying causes are not managed, it may lead to death in children with additional co-morbidities [11, 12]. Children with poor cognitive development have difficulties learning and perform poorly at school, thereby failing to reach their full potential [13]. Chronic helminth infection is also detrimental to the functioning of the immune response against infectious diseases such as TB and, hence, increases the risk of developing TB in later life [14]. Associations between TB and helminth infections have been reported for school-aged and adult populations [6, 15].

 Children living in resource-constrained areas in sub-Saharan Africa and elsewhere are at high risk of acquiring helminth infections, given their poor hygienic environments and unattended outdoor access when playing with peers. Early detection and effective management of

helminth infection can improve children's health and wellbeing. Most studies of helminth infections have focused on school-aged populations, though preschool-aged children in highly endemic areas might also show high infection rates [16]. For example, a community-based, cross-sectional survey conducted in Nairobi found that the soil-transmitted helminth prevalence among preschool-aged children was similar to that of school-aged children [17]. In 2008, the World Health Organization (WHO) set an ambitious goal to reach 100% anthelmintic drug coverage by 2012 in endemic countries [18]. Yet, the WHO did not include preschool-aged children in targeted deworming campaigns until 2008.

In 2009, Tanzania adopted the WHO initiative to integrate preventive chemotherapy into its neglected tropical diseases control program, which also covers helminthiases. To date, the focus has been on school-aged children and adults [19]. No universal guidelines exist for using chemotherapy to prevent various helminth infections in preschoolers. To assess the prevalence and intensity of helminth infections among preschool-aged children, including its impact on clinical outcomes, we conducted a cross-sectional survey in an urban setting in Temeke district, Dar es Salaam, Tanzania. We employed a suite of standardized, quality-controlled diagnostic methods to enhance the accuracy of species-specific helminth detection and quantification [20].

Methods

Ethics statement

The study was approved by the Institutional Review Board of the Ifakara Health Institute (reference no. IHI/IRB 12–2015), the Medical Research Coordinating Committee of the National Institute of Medical Research in Tanzania (reference no. NIMR/HQ/R.8a/Vol. IX/2002), and the Ethics Committee of Northwestern and Central Switzerland (reference no. EKNZ UBE-15/49). Children were enrolled after their parents or caregivers gave written informed consent.

Infections with *Schistosoma* spp. were treated with praziquantel (40 mg/kg), soil-transmitted helminths with albendazole (200 or 400 mg depending on children's age), and *Strongyloides stercoralis* with ivermectin (3 mg), immediately after diagnosis [21]. Additionally, children with a history of TB exposure without active disease were started on isoniazid preventive therapy (20 mg/kg) [22]. Children with anemia (hemoglobin <11 g/dl) were given iron or folic acid supplements, as clinically appropriate. In addition, dietary counseling was provided to parents and caregivers of all children with impaired nutritional status. Human immunodeficiency virus (HIV)-positive children were referred to a care and treatment center for further management, in line with Tanzanian guidelines.

Study setting

The study was carried out in the Temeke district, Dar es Salaam, Tanzania [7] between October 2015 and September 2016. The district has routine TB contact tracing in place supported by TB patients who successfully completed treatment. Mass deworming in the district is coordinated by the neglected tropical disease control coordinator. Although the local water authority supplies piped water to the district, due to the high demand, residents also use ground water sources from boreholes for household chores which is vulnerable to pollution from pit latrines. This borehole water is used by most of the residents in the district [23].

Study design

The current manuscript used the baseline data of a case-control study pertaining to the epidemiology of TB and helminth coinfections among children exposed and not exposed to TB.

Preschool-aged children were recruited from households with an adult TB case (sputum smear-positive for acid-fast bacilli) and from TB-free neighboring households (to serve as controls), based on previously described standard operating procedures [24]. In the present cross-sectional study embedded within the aforementioned case-control study, we assessed the prevalence of helminth infections and determined associations with household characteristics, child development and cognition, and hematological factors in the surveyed children.

Study population and sample size

We aimed for a sample size of 308 children, aged 6–59 months, with 154 TB-exposed and 154 TB-unexposed preschool-aged children, and with one child recruited per household. This sample size would allow estimating local helminth prevalence with a precision of 5% and at an error probability of 5% if the helminth prevalence were of the order of 30%.

Study procedures

Children were seen by trained study clinicians who collected sociodemographic and socioeconomic information and obtained their medical history, including prior illnesses and use of medication. Clinicians assessed children for TB signs and symptoms [22]. A TB-exposure score chart from South Africa was employed to assess TB exposure [25]. The TB score was then categorized into (i) not likely to have TB infection (score of 1–6), or (ii) presumptively TB infected (score of $\geq$7). In addition, all children had a chest X-ray done. Trained study nurses recorded anthropometric measurements (height and weight), collected samples (blood, urine, stool, adhesive tape slide, and induced sputum), and performed development and cognitive assessments (gross motor, fine motor, language, and social components).

On the day of enrollment, parents or caregivers were given two empty containers labeled with the participant's unique identification number and invited to submit one fresh morning stool sample and one urine sample of their child the following day. The samples were transferred to a nearby laboratory within 3 hours of collection. Due to limited financial and human resources, only a single stool and urine sample could be collected. Additionally, each participant was provided with a plastic pocket that contained an adhesive tape (50 x 20 mm) and a pre-labeled glass slide and asked to submit the slide with the anal adhesive tape for *Enterobius vermicularis* examination as described elsewhere [26]. We collected venous blood samples for full blood cell (FBC) counts and for malaria and HIV screening, along with induced sputum samples for microbiological investigation. All samples were received at Temeke clinic, transferred to a laboratory in appropriate temperature-controlled cooler boxes, and processed within 5 hours of receipt.

Cognitive assessment

A validated Malawi Development Assessment Tool (MDAT) that was translated into Kiswahili was used to assess children's development and cognition [27]. A medical doctor with expert training in pediatrics [28] trained the study nurses before commencing the study. Monthly refresher trainings were conducted on site for the duration of the study. Each child was assessed for 40 min. Parents or caregivers of acutely ill children were advised to return within a week of the child's recovery for assessment [28].

Laboratory procedures

Helminth investigations. A single stool sample was obtained from each child, subjected to triplicate Kato-Katz thick smears, and examined under a microscope by trained laboratory

technicians for species-specific diagnosis of helminth infection. Triplicate Kato-Katz thick smear slides and the FLOTAC methods were employed for the diagnosis of *Ascaris lumbricoides*, hookworm, *Hymenolepis diminuta*, *Schistosoma mansoni*, and *Trichuris trichiura* while the Baermann technique was used to detect larvae of *Strongyloides stercoralis* [29]. The adhesive tapes were examined under a microscope for *E. vermicularis* eggs [26]. To screen for *S. haematobium* eggs, urine samples underwent urine filtration in duplicates using a hydrophilic polycarbonate membrane filter with a pore size of 20 μm (Sterlitech; Kent, United States of America) and subsequent examination of the filters for *S. haematobium* eggs. Microhematuria was examined by reagent strips (Hemastix; Siemens Healthcare Diagnostics, Eschborn, Germany). Urine samples were additionally tested for *Schistosoma* spp. antigens using a point-of-care circulating cathodic antigen (POC-CCA) cassette test (Rapid Medical Diagnostics; Pretoria, South Africa) which has been primarily validated for *S. mansoni*, but cross-reactivity has been reported [20, 30]. Using a visual aid tool and based on a semi-quantitative score, the POC-CCA results were interpreted as negative, trace, 1+, 2+, or 3+. All slides with adhesive tapes, Kato-Katz thick smears, and urine filters were stored in boxes, and 10% of the slides were re-examined for quality control purposes by experienced laboratory technicians within 6 months [29]. All helminth investigations were conducted at the Bagamoyo Research and Training Centre. The standard operating procedures have been described in detail elsewhere [31].

Microbiological investigations. Xpert MTB/RIF (Cepheid; Sunnyvale, CA, United States of America) was performed on induced sputum samples at the Temeke district hospital laboratory to aid in the diagnosis of TB. The laboratory is continuously monitored for quality by the Central Tuberculosis Reference Laboratory (Dar es Salaam, Tanzania).

Blood testing. Blood samples were screened for malaria with a rapid diagnostic test (Access Bio; Somerset, NJ, United States of America), and for HIV infection using Alere Determine HIV-1/2 (Alere; Waltham, MA, United States of America) if the child's age was ≥18 months or RNA polymerase chain reaction if <18 months. The FBC were done with an MS4 Vet hematology analyzer (Diamond Diagnostics; Massachusetts, United States of America) to determine hematological indices such as hemoglobin, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and red blood cell distribution width (RCDW).

Data collection and definitions

Data were recorded into tablet computers, using open data kit (ODK; http://opendatakit.org/) and "odk_planner", a data management tool. Laboratory results were entered into ODK from paper forms.

A helminth infection was defined as positive when eggs or larvae of the following species were microscopically identified: *A. lumbricoides*, *E. vermicularis*, hookworm, *H. diminuta*, *S. haematobium*, *S. mansoni*, *S. stercoralis*, or *T. trichiura*. Subsequently, helminth infections were grouped into (i) schistosomiasis, defined as infection with either *S. mansoni* or *S. haematobium* (based on stool microscopy, using Kato-Katz thick smears, urine filtration and/or positive POC-CCA urine cassette test results) and (ii) other helminthiases, including infections with any of the other helminths (*A. lumbricoides*, *H. diminuta*, hookworm, *T. trichiura*, *E. vermicularis*, and *S. stercoralis*). A POC-CCA test was regarded as positive if the band revealed 1+, 2+, or 3+. In sensitivity analyses, POC-CCA definition included also trace-positive results.

In the absence of any signs or symptoms suggestive of TB and/or as ascertained by Xpert MTB/RIF, a child was considered presumptively TB infected if the TB exposure score was ≥7 and unlikely to have a TB infection if the score was 1–6 [25]. Anemia was defined as hemoglobin <11.0 g/dl, as per WHO recommendations [32]. Anthropometric z-scores were calculated

using the 2006 WHO Growth Standards in Stata version 13.1 (Stata Corporation; College Station, TX, United States of America) using the 'zscore06' command [33].

Statistical analysis

Absolute frequencies and proportions were used to describe children, parents/caretakers, and household characteristics overall and stratified by the two groups of helminthiases. A measure of socioeconomic status was derived from a factor analysis of household asset variables and defined as low or high for score values below and above the median, respectively. Clinical outcomes included anemia, cognitive score and anthropometric measures (weight and height). We performed mixed logistic regression analyses with random intercepts at the level of matched pairs to identify risk factors for helminth infection, considering schistosomiasis and other helminthiases. We constructed multivariable core models comprising age, sex, type of toilet, hygiene behavior, and parent education variables based on clinical relevance and added other variables as appropriate, one by one. We also performed a sensitivity analysis to identify risk factors for *Schistosoma* spp. infection using the core model as above and considering trace results in the POC-CCA urine cassette test as positive. We used box-plots to compare the four MDAT components in children with and without helminth infections and calculated the overall median and interquartile range (IQR) of the total MDAT score and across relevant subsamples. We dichotomized the four components of the MDAT score at their median and ran mixed logistic regressions to compare scores between helminth-infected and uninfected children. We also compared hematological indices according to the presence of helminth infections using mixed linear regression models. All analyses were performed in Stata version 13.1 (Stata Corporation; College Station, United States of America).

Results

Study flow and baseline characteristics of children

We invited 398 parents and caregivers with children aged 6–59 months to participate. Parents/caregivers of 325 children consented and their children were enrolled. Of those, 310 completed the study procedures. Eight children did not provide their sociodemographic and clinical information, six did not submit stool and urine samples for helminth diagnosis, and one parent withdrew consent (Fig 1).

Of the 310 participating children, 160 (52%) were girls and the median age was 26 months (IQR: 17–42 months, range 6–58 months). The median height-for-age Z-score (HAZ) was -1.14 (95% confidence interval (CI): -1.91 to -0.20) (Table 1). A total of 189 (61%) children were exposed to smear-positive adult pulmonary TB patients and four (1.3%) were HIV-positive. Twenty-nine (9.4%) mothers reportedly tested HIV-positive during pregnancy. Fourteen (4.5%) children had a positive malaria rapid diagnostic test, six (1.9%) reportedly received anthelmintics within 3 months prior to enrollment in the study. Parents/caretakers of 23 (7.4%) children reported having moved from other regions to Dar es Salaam after their children were born.

Prevalence of helminth infections

The overall prevalence of *Schistosoma* spp. infection was 15.8% (95% CI 12.1–20.3%). *Schistosoma* spp. infection as determined by POC-CCA, was found in 47 children (15.2%; 95% CI 11.6–19.6%), *S. haematobium* eggs were only found in the urine of three individuals (1.0%) (Table 2), and no *S. mansoni* eggs were found in any of the Kato-Katz thick smears or FLOTAC examinations. There was no difference in the distribution of children with *Schistosoma*
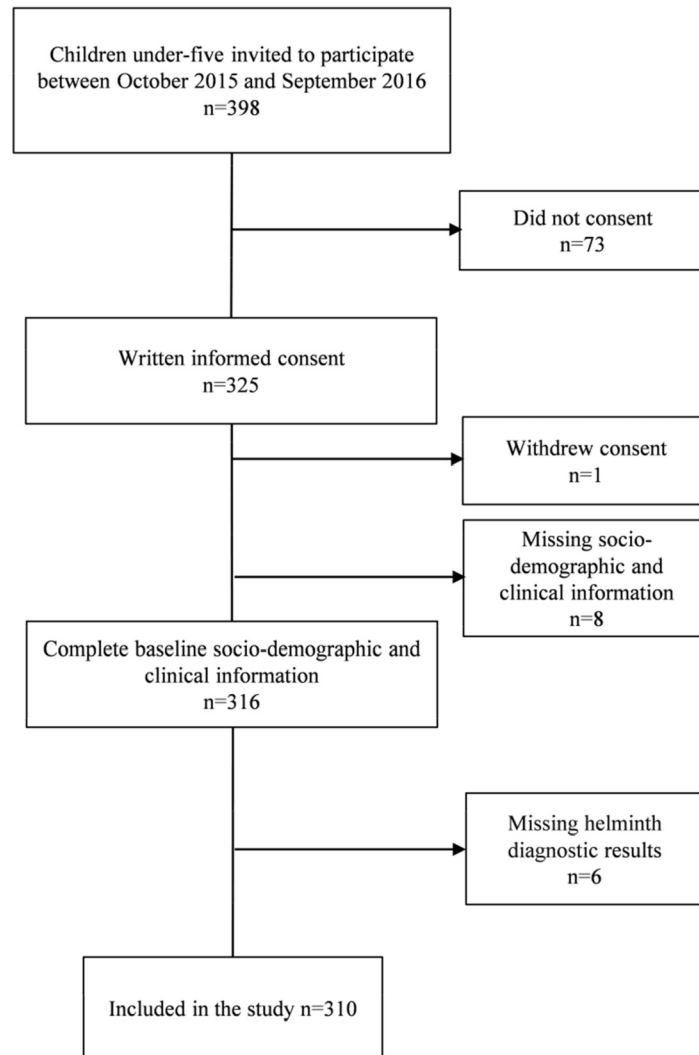
Fig 1. Flow chart of the 310 participants included in the study.

spp. infection in young (6–24 months) and older (25–59 months) age groups (53% *vs.* 47%, p = 0.3) or between boys and girls (51% *vs.* 49%, p = 0.7). There was also no significant difference between TB-exposed and unexposed children (67% *vs.* 60%, p = 0.3), as shown in Table 1. The prevalence of *Schistosoma* spp. infection (as determined by POC-CCA) increased to 31.0% (95% CI 26.3–36.7%) when considering trace results as positive.

The prevalence of other helminth species infections, excluding *Schistosoma* spp., was 9.0% (95% CI 6.3–12.8%). The most frequently detected helminth species was *S. stercoralis* (16 children; 5.2%), followed by *E. vermicularis* (6; 1.9%), and hookworm (6; 1.9%). Infections with *A. lumbricoides* and *H. diminuta* were found in only one child each, and no *T. trichiura* infection was observed (Table 2). The difference in the distribution of helminth infections between TB-exposed and unexposed children was not statistically significant (62% *vs.* 54%, p = 0.4).

Five children (1.6%) had dual species helminth infections: two with *Schistosoma* spp.-*S. stercoralis*; and one each with *Schistosoma* spp.-*E. vermicularis*, *E. vermicularis*-hookworm, and *A. lumbricoides*-*H. diminuta*. One child had a triple species helminth infection with *Schistosoma* spp.-*E. vermicularis*-hookworm.

Table 1. Baseline sociodemographic, socioeconomic, and clinical characteristics of 310 preschool-aged children in a study conducted between October 2015 and September 2016, and their parents/caregivers in the Temeke district, Dar es Salaam, Tanzania.

Characteristic	All	Any helminth species [1]		Schistosoma spp. [2]	
n (%)	(n = 310)	Infected (n = 74)	Not infected (n = 236)	Infected (n = 49)	Not infected (n = 261)
Child characteristics					
Age (months), median (IQR)	26 (17–42)	23 (17–36)	28 (17–43)	23 (18–38)	27 (16–42)
Age groups (months)					
6–12	52 (17)	11 (15)	41 (17)	8 (16)	44 (17)
13–24	92 (30)	29 (39)	63 (27)	18 (36)	74 (28)
25–36	71 (23)	16 (22)	55 (23)	10 (21)	61 (24)
37–48	57 (18)	10 (14)	47 (20)	7 (14)	50 (19)
49–59	38 (12)	8 (11)	30 (13)	6 (13)	32 (12)
Sex					
Female	160 (52)	37 (50)	123 (52)	24 (49)	136 (52)
Male	150 (48)	37 (50)	113 (48)	25 (51)	125 (48)
Delivered by					
Caesarean section	40 (13)	13 (17)	27 (11)	10 (20)	30 (12)
SVD	253 (20)	56 (76)	197 (84)	38 (76)	215 (82)
Unknown	17 (5)	5 (7)	12 (5)	1 (2)	16 (6)
Born at gestation age (weeks)					
Pre-term <37	9 (3)	2 (2)	7 (3)	1 (2)	8 (3)
Term ≥37	284 (92)	67 (91)	217 (90)	45 (96)	239 (91)
Unknown	17 (5)	5 (7)	12 (5)	1 (2)	61 (6)
Birth weight (kg)					
Low <2.5	28 (9)	5 (7)	24 (10)	4 (8)	25 (10)
Normal ≥2.5	265 (86)	64 (86)	200 (85)	44 (09)	220 (84)
Unknown	17 (5)	5 (7)	12 (5)	1 (2)	16 (6)
Immunization status					
BCG, with scar	306 (99), 260 (85)	71 (96)	235 (99)	42 (86)	218 (84)
Measles	263 (85)	68 (92)	195 (83)	46 (94)	217 (83)
HIV status					
Positive	4 (1.3)	2 (3)	2 (1)	0	4 (2%)
Negative	306 (98.7)	72 (97)	234 (99)	49 (100)	257 (98)
Hemoglobin level (g/dl)					
Anemic <11.0	203 (65)	56 (76)	147 (62)	35 (71)	168 (64)
Not anemic ≥11.0	104 (34)	17 (23)	87 (37)	13 (27)	91 (35)
Missing	3 (1)	1 (1)	2 (1)	1 (2)	2 (1)
Malaria rapid diagnostic test					
Positive	14 (5)	3 (4)	11 (5)	3 (6)	11 (4)
Negative	296 (95)	71 (96)	225 (95)	46 (94)	250 (96)
TB exposure history					
Exposed	189 (61)	46 (62)	143 (61)	33 (67)	156 (60)
Unexposed	121 (39)	28 (38)	93 (39)	16 (33)	105 (40)
TB exposure score					
Likely not infected	197 (64)	50 (68)	147 (62)	33 (67)	164 (63)
Likely infected	113 (36)	24 (32)	89 (38)	16 (33)	97 (37)
Deworming status (past 3 months)					
Not dewormed	304 (98)	72 (97)	232 (98)	48 (98)	256 (98)
Dewormed	6 (2)	2 (3)	4 (2)	1 (2)	5 (2)

(*Continued*)

Table 1. (*Continued*)

Characteristic	All	Any helminth species [1]		Schistosoma spp. [2]	
n (%)	(n = 310)	Infected (n = 74)	Not infected (n = 236)	Infected (n = 49)	Not infected (n = 261)
HAZ-scores					
Median (IQR)	-1.14 (-1.91 to -0.2)	-1.16 (-1.72 to -0.07)	-1.12 (-1.94 to -0.33)	-1.17 (-1.58 to -0.13)	-1.09 (-1.98 to -0.31)
WAZ-score					
Median (IQR)	-1.14 (-2.07 to -0.35)	-1.3 (-2.22 to -0.28)	-1.12 (-1.99 to -0.35)	-1.34 (-2.36 to -0.69)	-1.10 (-2.05 to -0.33)
WHZ-score					
Median (IQR)	-0.94 (-2.02 to -0.13)	-1.16 (-2.02 to -0.17)	-0.79 (-1.86 to -0.13)	-1.48 (-2.07 to -0.10)	-0.75 (-1.83–15.0)
Household characteristics					
Number of people					
<6	190 (61)	43 (58)	147 (62)	29 (59)	161 (62)
≥6	120 (39)	31 (42)	89 (38)	20 (41)	100 (38)
Household income per month (US$)					
<100	108 (35)	28 (38)	80 (34)	15 (31)	93 (36)
≥100	202 (65)	46 (62)	156 (66)	34 (69)	168 (64)
Water source for household chores					
Bore well	90 (29)	15 (20)	27 (11)	14 (29)	28 (11)
Tap	153 (49)	43 (58)	158 (67)	27 (55)	174 (67)
Unknown	67 (22)	16 (22)	51 (22)	8 (16)	59 (22)
Type of household toilet					
Septic tank	93 (30)	28 (38)	65 (28)	21 (43)	72 (28)
Pit latrine	217 (70)	46 (62)	171 (72)	28 (57)	189 (72)
Hygienic practices					
Poor	36 (12)	12 (16)	24 (10)	7 (14)	29 (11)
Good	274 (88)	62 (84)	212 (90)	42 (86)	232 (89)
SES					
Low	159 (50)	40 (54)	119 (50)	28 (57)	131 (50)
High	151 (50)	34 (46)	127 (50)	21 (43)	130 (50)
Parent/caregiver characteristics					
Mothers prior pregnancies					
Unknown	17 (5)	5 (7)	12 (5)	1 (2)	16 (6)
0	88 (30)	19 (26)	69 (29)	9 (19)	79 (30)
1–2	142 (48)	39 (53)	103 (44)	30 (64)	112 (43)
≥3	63 (17)	11 (15)	52 (22)	7 (15)	56 (21)
Mothers HIV status during pregnancy					
Unknown	24 (8)	6 (8)	18 (7)	1 (2)	23 (9)
Positive	29 (9)	4 (5)	25 (11)	3 (6)	26 (10)
Negative	257 (83)	64 (86)	193 (82)	45 (92)	212 (81)
Mothers marital status					
Single	76 (25)	19 (25)	57 (24)	14 (29)	62 (24)
Married	217 (70)	50 (68)	167 (71)	34 (69)	183 (70)
Unknown	17 (5)	5 (7)	12 (5)	1 (2)	16 (6)
Parent education level					
No or primary education	244 (79)	63 (85)	181 (77)	42 (86)	202 (77)
Secondary/higher education	66 (21)	11 (15)	55 (23)	7 (14)	59 (23)

(*Continued*)

Table 1. (*Continued*)

Characteristic	All	Any helminth species [1]		*Schistosoma* spp. [2]	
n (%)	(n = 310)	Infected (n = 74)	Not infected (n = 236)	Infected (n = 49)	Not infected (n = 261)
Parent occupation					
Unemployed	196 (63)	49 (66)	147 (62)	31 (63)	165 (63)
Employed	114 (37)	25 (34)	89 (38)	18 (37)	96 (37)
Family migration history since child birth					
Migrated	23 (7)	8 (11)	15 (6)	3 (6)	20 (8)
Did not migrate	189 (61)	44 (59)	144 (61)	36 (73)	153 (58)
Unknown	98 (32)	22 (30)	77 (33)	10 (20)	88 (34)

HAZ, height for age, moderate to severe stunting (z-score≤-2); HIV, human immunodeficiency virus; TB exposure score based on Mandalakas et al. [25]; SVD, spontaneous vaginal delivery; WAZ, weight for age, moderate to severe underweight (z-score≤-2); WHZ, weight for height, moderate to severe wasting (z-score≤-2); US$, United States dollars (1 US$ = 2,190 Tanzanian Shillings); SES, socioeconomic status (low = below median of the principal asset score, high = above the median of the principal asset score)

[1] Any helminth infection defined as positive when eggs or larvae of the following species were microscopically identified: *A. lumbricoides*, *E. vermicularis*, hookworm, *H. diminuta*, *S. haematobium*, *S. mansoni*, *S. stercoralis*, or *T. trichiura*; or a positive POC-CCA urine cassette test result indicating *Schistosoma* spp. infection (test result 1+, 2+, or 3+)

[2] *Schistosoma* spp. includes *S. mansoni* and *S. haematobium*

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Risk factors for helminth infections

Schistosoma spp. infection was significantly associated with having a septic tank toilet in the household (adjusted odds ratio (aOR) 2.04, 95% CI: 1.02–4.07, p = 0.042; Table 3). Higher education of parents/caregivers, tap water at home, and better hygiene practices showed no significant association with *Schistosoma* spp. infection. Additionally, *Schistosoma* spp. infection was similar in TB-exposed and unexposed children (aOR 1.34, 95% CI: 0.67–2.68, p = 0.4) (Table 3). In the sensitivity analysis that considered POC-CCA trace results as positive, none of the variables included in the core model, including having septic tank toilets, were associated with *Schistosoma* spp. infection (S1 Table). Furthermore, none of the risk factors were significantly associated with any of the other helminth infection, including having a septic tank toilet (aOR 0.92, 95% CI: 0.35–2.40, p = 0.9) (Table 3).

Association of helminth infections with development and cognitive scores

The overall median MDAT score in the study population was 3.30 (IQR 2.78–3.49). There was no significant difference in the overall median cognitive score in helminth-infected and uninfected children (3.20 [95% CI 2.74–3.44] *vs.* 3.33 [95% CI 2.80–3.50], p = 0.2 (S2 Table). There was also no effect of *Schistosoma* spp. infection on the overall median cognitive score among the two groups (3.17 [95% CI 2.78–3.44] *vs.* 3.32 [95% CI 2.78–3.50], p = 0.2).

The median gross motor score tended to be higher among preschool-aged children with a helminth infection compared to their uninfected peers. The median fine motor (0.79 *vs.* 0.83), social (0.85 *vs.* 0.89), and language scores (0.86 *vs.* 0.88) tended to be lower among helminth-infected compared to helminth-uninfected children (Fig 2), but none of the differences achieved statistical significance.

Table 2. Frequency distribution of helminth species among preschool-aged children in Dar es Salaam, Tanzania in a study conducted between October 2015 and September 2016.

Helminth infection	All	≤24 months		>24 months	
		Male	Female	Male	Female
	n (%)	n (%)	n (%)	n (%)	n (%)
Total	310 (100)	72 (100)	72 (100)	78 (100)	88 (100)
Any helminth infection [1]	74 (23.9)	25 (34.7)	15 (20.8)	12 (15.4)	22 (25.0)
Schistosomiasis					
Schistosoma **spp. (POC-CCA) [2]**					
Any positive result (trace and positive)	97 (31.3)	27 (37.5)	21 (29.2)	20 (25.6)	29 (33.0)
Trace	50 (16.1)	11 (15.3)	12 (16.7)	11 (14.1)	16 (18.2)
Positive	47 (15.2)	16 (22.2)	9 (12.5)	9 (11.5)	13 (14.3)
1+	34 (11.0)	8 (11.1)	9 (12.5)	6 (7.7)	11 (12.5)
2+	12 (3.9)	8 (11.1)	0 (0.0)	2 (2.6)	2 (2.3)
3+	1 (0.3)	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)
Schistosoma haematobium **[3]**					
Positive	3 (0.97)	1 (1.5)	1 (1.5)	0 (0.0)	1 (1.1)
Other helminth infection [4]					
Any of the other helminth species	28 (9.0)	10 (13.9)	5 (6.9)	4 (5.1)	9 (10.2)
Strongyloides stercoralis	16 (5.2)	6 (8.3)	3 (4.2)	3 (3.9)	4 (4.6)
Enterobius vermicularis	6 (1.9)	1 (1.4)	1 (1.4)	1 (1.3)	3 (3.4)
Hookworm	6 (1.9)	3 (4.2)	2 (2.8)	0 (0.0)	1 (1.1)
Ascaris lumbricoides	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)
Hymenolepis diminuta	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)

[1] Any helminth was defined as positive when eggs or larvae of the following species were microscopically identified: *A. lumbricoides*, *E. vermicularis*, hookworm, *H. diminuta*, *S. haematobium*, *S. mansoni*, *S. stercoralis*, and *T. trichiura*

[2] Point-of-care circulating cathodic antigen urine cassette test for detection of *Schistosoma* spp. infection (POC-CCA test result 1+, 2+, or 3+).

[3] Based on urine filtration (egg-positive urine filtration)

[4] Other helminth species (based on stool or adhesive tape microscopy): *A. lumbricoides*, *E. vermicularis*, hookworm, *H. diminuta*, and *S. stercoralis*

Five participants had dual species and one participant a triple species helminth infection

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Association of helminth infection with hematological parameters

Almost two-third of the children (203; 65%) were anemic; nine (4.4%) of those with anemia had a positive rapid malaria diagnostic test result. Moderate anemia (hemoglobin level 7.0–9.9 g/dl) was most prevalent (49%), while mild anemia (hemoglobin 10.0–10.9 g/dl) was found in 44%, and severe anemia (hemoglobin <7 g/dl) was found in 14 of the anemic children (6.9%). Five (6%) children with mild anemia, three (3%) with moderate anemia, and one (7%) with severe anemia had malaria.

Anemia was diagnosed in 56 (77%) participants with helminth infections, including all six with hookworm, all three with *S. haematobium*, the one with *A. lumbricoides*, and the one with *H. diminuta*. With regard to *Schistosoma* spp. infection (as determined by POC-CCA), 33 out of 46 infected had anemia (72%) and 12 of the 16 *S. stercoralis*-infected children were anemic (75%). Two children with anemia had both helminth infections and malaria.

When comparing hemoglobin and hematological parameters with helminth infection, the median hemoglobin value was significantly lower in helminth-infected children compared with their uninfected peers (10.1 g/dl [IQR 9.1–10.8 g/dl] *vs.* 10.4 g/dl [IQR 9.4–11.4 g/dl], p = 0.027) (Fig 3). This difference remained significant even when excluding malaria cases (10.4 g/dl [IQR 9.6–11.4 g/dl] *vs.* 10.1 g/dl [IQR 9.0–10.8], p = 0.014). All other hematological

Table 3. Risk factors for *Schistosoma* and soil-transmitted helminth infections among preschool-aged children in Dar es Salaam, Tanzaniain a study conducted between October 2015 and September 2016.

Characteristics	All	*Schistosoma* spp.				Other helminths			
	n (%)	Crude		Adjusted		Crude		Adjusted	
		OR (95% CI)	p value	aOR (95% CI)	p value	OR (95% CI)	p value	aOR (95% CI)	p value
Age groups (months)			0.5		0.5		0.3		0.3
6–12	52 (17)	1.00		1.00		1.00		1.00	
13–24	92 (30)	1.33 (0.21–3.40)		1.31 (0.51–3.40)		2.36 (0.56–9.86)		2.38 (0.58–9.78)	
25–36	71 (23)	0.89 (0.31–2.51)		0.86 (0.30–2.44)		2.00 (0.45–8.92)		1.91 (0.44–8.36)	
37–48	57 (18)	0.76 (0.25–2.34)		0.76 (0.24–2.37)		0.80 (0.13–4.78)		0.78 (0.13–4.59)	
49–59	38 (12)	1.00 (0.31–3.32)		0.92 (0.27–3.11)		0.80 (0.11–5.83)		0.80 (0.11–5.72)	
Sex			0.7		0.8		0.7		0.8
Female	160 (52)	1.00		1.00		1.00		1.00	
Male	150 (48)	1.12 (0.59–2.11)		1.06 (0.55–2.02)		1.16 (0.47–2.85)		1.05 (0.44–2.51)	
Individual deworming history[1]			0.9		0.9		0.6		0.6
Not dewormed	304 (98)	1.00		1.00		1.00		1.00	
Dewormed	6 (2)	1.07 (0.11–10.12)		1.06 (0.11–10.1)		2.14 (0.17–26.84)		2.24 (0.18–27.20)	
TB exposure			0.3		0.4		0.5		0.6
Unexposed	121 (39)	1.00		1.00		1.00		1.00	
Exposed	189 (61)	1.43 (0.73–2.82)		1.34 (0.67–2.68)		0.72 (0.31–1.67)		0.74 (0.31–1.74)	
Number of people in the household			0.7		0.7		0.4		0.4
<6	190 (61)	1.00		1.00		1.00		1.00	
≥6	120 (39)	1.13 (0.59–2.16)		1.13 (0.58–2.20)		1.47 (0.61–3.53)		1.49 (0.62–3.54)	
Water source for household chores			0.2		0.3		0.3		0.3
Bore well	90 (29)	1.00		1.00		1.00		1.00	
Tap	153 (49)	0.43 (0.21–0.88)		0.43 (0.20–0.94)		4.02 (1.04–15.5)		4.12 (1.05–16.3)	
Unknown	67 (22)	0.41 (0.16–1.02)		0.41 (0.16–1.08)		4.22 (0.96–18.5)		4.90 (1.07–22.3)	
Type of toilet			0.04		0.04		0.9		0.9
Pit latrine	217 (70)	1.00		1.00		1.00		1.00	
Septic tank	93 (30)	2.03 (1.03–4.00)		2.04 (1.02–4.07)		0.98 (0.37–2.57)		0.92 (0.35–2.40)	
Hygienic practices[2]			0.5		0.8		0.3		0.3
Poor	36 (12)	1.00		1.00		1.00		1.00	
Better	274 (88)	0.74 (0.29–1.87)		0.87 (0.34–2.25)		0.55 (0.17–1.82)		0.54 (0.16–1.78)	
Household income per month (US$)[3]			0.5		0.3		0.3		0.4
<100	108 (35)	1.00		1.00		1.00		1.00	

(*Continued*)

Table 3. (*Continued*)

Characteristics	All	*Schistosoma* spp.				Other helminths			
	n (%)	Crude		Adjusted		Crude		Adjusted	
		OR (95% CI)	p value	aOR (95% CI)	p value	OR (95% CI)	p value	aOR (95% CI)	p value
≥100	202 (65)	1.25 (0.63–2.45)		1.56 (0.78–3.13)		0.61 (0.26–1.44)		0.71 (0.29–1.73)	
Parent education level			0.2		0.2		0.4		0.5
No or primary education	244 (79)	1.00		1.00		1.00		1.00	
Secondary/higher education	66 (21)	0.57 (0.24–1.36)		0.53 (0.22–1.28)		0.60 (0.18–1.97)		0.63 (0.19–2.09)	
Parent occupation			0.9		0.7		0.4		0.5
Housewife/unemployed	196(63)	1.00		1.00		1.00		1.00	
Employed	114(37)	1.01 (0.52–1.96)		0.85 (0.42–1.76)		0.65 (0.25–1.66)		0.70 (0.26–1.92)	
Family migration history since child birth			0.08		0.1		0.07		0.1
Migrated	23 (7)	1.00		1.00		1.00		1.00	
Did not migrate	189 (61)	1.58 (0.43–5.84)		1.55 (0.41–5.80)		4.74 (1.28–17.63)		5.30 (1.43–9.74)	
Unknown	98(32)	0.74 (0.18–3.09)		0.74 (0.18–3.10)		2.24 (0.89–5.63)		2.04 (0.80–5.18)	

Schistosomiasis includes *S. mansoni* and *S. haematobium* (positive POC-CCA urine cassette test results 1+, 2+, or 3+ and egg-positive urine filtration); other helminth species (based on stool microscopy) include *A. lumbricoides*, *E. vermicularis*, hookworm, *H. diminuta*, and *S. stercoralis*

[1] Past 3 months

[2] Hygiene practice: parent/caregiver always wash fruits or vegetables before giving to children

[3] US$, United States dollars (1 US$ = 2,190 Tanzanian shillings)

Multivariable mixed logistic regression model with random intercepts at the level of matched pairs, containing the respective variable along with age, sex, and type of toilet
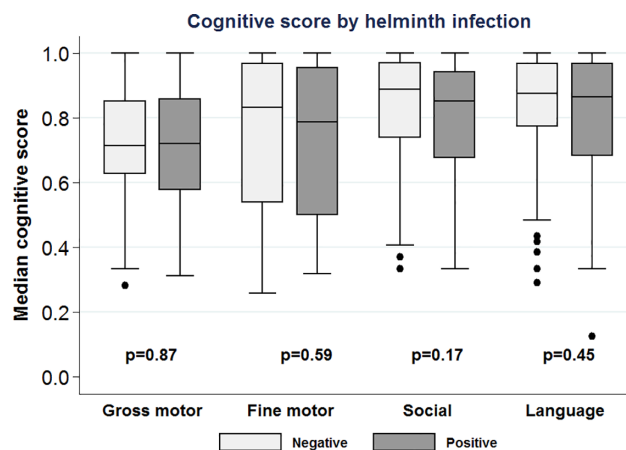
Fig 2. Box-plots comparing development and cognitive function among children with and without helminth infection.
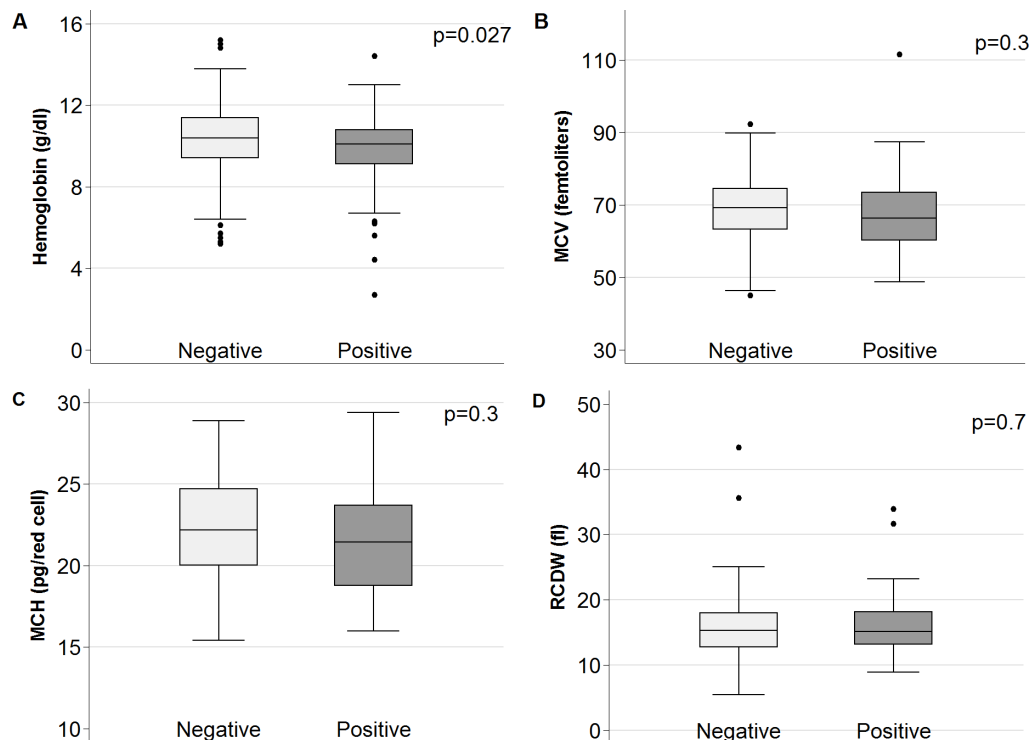
Fig 3. Box plots showing distribution of hemoglobin and red blood cell indices among children with (n = 73) and without helminth infection (n = 234). A) Distribution of hemoglobin by helminth infection; B) distribution of mean corpuscular volume by helminth infection; C) distribution of mean corpuscular hemoglobin by helminth infection; and D) distribution of red blood cell distribution width by helminth infection.

parameters (MCV, MCH, and RCDW) were equally distributed between helminth-infected and uninfected children.

Discussion

We present findings on the prevalence, clinical relevance, and risk factors associated with helminth infection among preschool-aged children in a poorly planned and under-resourced district in the coastal region of Dar es Salaam, Tanzania. We found that the prevalence of *Schistosoma* spp. was high (16.0%) among children under the age of 5 years, but the prevalence of other helminth infections was relatively low. We found no positive associations between helminth infections and commonly reported risk factors or development/cognitive scores. Anemia was a common clinical presentation and more frequent among children infected with helminths than their non-infected counterparts.

To our knowledge, this is the first study to report such a high prevalence of *Schistosoma* spp., as determined by the POC-CCA urine cassette test among preschool-aged children in the coastal urban area of Dar es Salaam. The POC-CCA is considered a highly sensitive rapid diagnostic test and was primarily developed for the detection of *S. mansoni* [20]. In Tanzania, the POC-CCA has previously been used among preschool-aged children to detect *S. mansoni*, reporting a high prevalence of up to 50% in well-known high-risk *S. mansoni* areas around Lake Victoria (North-Western part of Tanzania), where the natural open freshwater serves as a habitat for the intermediate host snails [34, 35]. However, a recent systematic review highlighted a low specificity of the POC-CCA test assay in detecting *S. mansoni* (as compared with stool microscopy) and/or the possibility of cross-reactivity of the assay with *S. haematobium*

[30]. In our study, the positive POC-CCA results were not confirmed by stool microscopy, since the commonly used Kato-Katz method failed to identify any *S. mansoni* eggs in our study population. Furthermore, the urine filtration only revealed a very low prevalence of *S. haematobium* (1.0%). Similarly, in a recent investigation in Dar es Salaam that used Kato-Katz and urine filtration but not the POC-CCA, the prevalence of *S. haematobium* among school-aged children was reported to be 1.2%, while no *S. mansoni* was reported [36]. Likely, the conventional stool and urine examination underestimate the true prevalence due to their low sensitivity to detect light intensity infection as they might occur in young children. However, an overestimation of *Schistosoma* spp. prevalence by a potential cross-reactivity of the POC-CCA with other conditions can also not be fully ruled out [30].

Urban schistosomiasis caused by *S. mansoni* has been reported elsewhere, including Brazil [37], Côte d'Ivoire [38] and Tanzania [39], but most of these studies did not include preschool-aged children. However, intense transmission of *S. mansoni* has never been formally demonstrated in urban regions of Tanzania such as Dar es Salaam [40, 41]. Dar es Salaam is a coastal city along the Indian Ocean and it was known to have a high prevalence and transmission of *S. haematobium* since the 1980s [34, 40]. Our study showed that the prevalence of *S. haematobium* and *S. mansoni* infection as determined by egg counts in urine and stool is low, while the POC-CCA suggests that infections due to *Schistosoma* spp. have a considerably higher prevalence. Further studies using highly sensitive and specific tests for schistosomiasis diagnosis in coastal Tanzania involving different age and population groups should be conducted to establish the species- and age-specific prevalence as the global focus is shifting toward disease elimination.

Overall, the prevalence of other helminth infections was found to be lower than that reported in other under-resourced settings [16, 42]. Ten years ago, a study in two district hospitals in Dar es Salaam reported a soil-transmitted helminth prevalence (including hookworm, *A. lumbricoides*, and *T. trichiura*) of 33% among children below the age of 5 years [43]. The lower rates noted in our study may be due to an improved socioeconomic status among the general population and/or to successful biannual preventive chemotherapy campaigns, initiated in 2004, that include administering mebendazole and vitamin A supplementation to preschool-aged children [44].

We did not find any association between helminth infections and commonly reported risk factors such as age, hygiene, low socioeconomic status, and history of migration. This is in contrast to other studies, which identified age, poor hygiene, and low socioeconomic status as risk factors for helminth infection in children [16, 17, 35, 45]. The lack of association with risk factors might be in part due to our sampling strategy, which was primarily powered to detect the prevalence of helminth infection among our study population, rather than association with risk factors. Although we identified having toilets with septic tanks as a risk factor for *Schistosoma* spp. infection, this association lacked statistical significance after including POC-CCA trace results. We did not find evidence of an association between helminth infection and TB exposure. To our knowledge, no study has yet specifically investigated schistosomiasis and TB in preschool-aged children. However, a study in Kenya reported increased odds of hookworm infection among school-aged children with latent TB infection compared to unexposed controls [6]. It will be important to further elucidate the impact of helminth co-infections in early childhood on developing TB.

We documented a high prevalence of anemia among preschool-aged children that was associated with helminth infection. Similar findings have been reported in studies from Ethiopia and Nigeria, where children who were infected with two or more helminth species were at higher risk of having anemia [46]. High prevalence of anemia among preschool-aged children might also be caused by poor diets, low socioeconomic status of parents or caregivers, as indicated by the high rate of unemployment [23, 47]. Other assessed hematological parameters

were not associated with helminth infection, possibly due to low prevalence and intensity of helminth infection as well as to the good nutritional status among children evidenced by HAZ and WAZ in our study [48]. Previous research showed that heavy helminth infection impairs development and cognition [10,49]. In our study, helminth infection was not associated with reduced development and cognition. However, such differences may be seen only over longer time frames during detailed follow-up surveys.

Our study has strengths and limitations that warrant further consideration. We systematically screened for helminthiases and other diseases, such as malaria, HIV, and active TB, using a suite of standardized and quality-controlled diagnostic tests [25, 34, 50]. These infectious diseases all contribute to high morbidity and mortality among children <5 years [11]. The main limitations of our study include sampling households based on TB exposure (given that the overall study aim was to explore interactions of TB and helminth co-infections), and restricting the study area to an urban setting. However, poorly planned urban settings have the highest population growth in sub-Saharan Africa with considerable disease burdens of major infectious and non-communicable diseases [51].

In conclusion, our study showed high prevalence of *Schistosoma* spp. infection as determined by the POC-CCA urine cassette test, among preschool-aged children, even in a highly urbanized setting in East Africa, an observation that has not been previously reported. It must be noted though that this result was achieved with a highly sensitive diagnostic assay, namely, the POC-CCA urine cassette test. Cross-reactivity with other conditions cannot be ruled out. Helminth infections were associated with anemia, but not with growth development and development of cognitive functions among our group of young children. However, the fact that helminth infection was not shown to affect children's development and cognition does not mean they will not be affected later in life. With the WHO's ambitious goal of reaching 100% coverage of preventive chemotherapy targeting major helminthiases, our findings call for urgent planning and implementation of specific interventions to prevent further morbidity, and to improve health, care, and wellbeing of these young children. Deworming likely reduces the prevalence of anemia, improves children's development and cognition, and prevents complications later in life [46, 52]. Future research to confirm our findings using newly developed and highly sensitive and specific test assays, to identify and map *Schistosoma* spp. infection hotspots and its intermediate host snails in Dar es Salaam are needed to design targeted interventions for effectively controlling morbidity due to schistosomiasis and shift toward interruption of transmission.

Supporting information

S1 Checklist. STROBE checklist.
(DOCX)

S1 Table. Additional analysis: Risk factors for *S. mansoni* infection (defined trace results as positive based on point-of-care circulating cathodic antigen (POC-CCA) urine cassette test) among 310 under-five children in Temeke district, Dar es Salaam, Tanzania.
(DOCX)

S2 Table. Comparison of cognitive score among helminth-infected and non-infected preschool-aged children in Dar es Salaam, Tanzania.
(DOCX)

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Author Contributions

References

1. Utzinger J, Becker SL, Knopp S, Blum J, Neumayr AL, Keiser J, et al. Neglected tropical diseases: diagnosis, clinical management, treatment and control. Swiss Med Wkly. 2012; 142:w13727. Epub 2012/11/28. https://doi.org/10.4414/smw.2012.13727 PMID: 23180107.

2. Pullan RL, Smith JL, Jasrasaria R, Brooker SJ. Global numbers of infection and disease burden of soil transmitted helminth infections in 2010. Parasit Vectors. 2014; 7:37. Epub 2014/01/23. https://doi.org/10.1186/1756-3305-7-37 PMID: 24447578; PubMed Central PMCID: PMCPMC3905661.

3. Hotez PJ, Molyneux DH, Fenwick A, Kumaresan J, Ehrlich Sachs S, Sachs JD, et al. Control of neglected tropical diseases. N Engl J Med. 2007; 357:1018–27. Epub 2007/09/07. https://doi.org/10.1056/NEJMra064142 PMID: 17804846.

4. Bartram J, Cairncross S. Hygiene, sanitation, and water: forgotten foundations of health. PLoS Med. 2010; 7:e1000367. Epub 2010/11/19. https://doi.org/10.1371/journal.pmed.1000367 PMID: 21085694; PubMed Central PMCID: PMCPMC2976722.

5. Thomas TA, Mondal D, Noor Z, Liu L, Alam M, Haque R, et al. Malnutrition and helminth infection affect performance of an interferon gamma-release assay. Pediatrics. 2010; 126(6):e1522–9. https://doi.org/10.1542/peds.2010-0885 PMID: 21059723

6. Sachiyo Nagi MI. Relationship between *Mycobacterium tuberculosis* and hookworm infections among school children in Mbita, Kenya. J Trop Dis. 2013;(03). https://doi.org/10.4172/2329-891X.1000120

7. Mhimbira F, Hella J, Said K, Kamwela L, Sasamalo M, Maroa T, et al. Prevalence and clinical relevance of helminth co-infections among tuberculosis patients in urban Tanzania. PLoS Negl Trop Dis. 2017; 11(2):e0005342. Epub 2017/02/09. https://doi.org/10.1371/journal.pntd.0005342 PMID: 28178325.

8. Lustigman S, Prichard RK, Gazzinelli A, Grant WN, Boatin BA, McCarthy JS, et al. A research agenda for helminth diseases of humans: the problem of helminthiases. PLoS Negl Trop Dis. 2012; 6(4):e1582.

https://doi.org/10.1371/journal.pntd.0001582 PMID: 22545164; PubMed Central PMCID: PMCPMC3335854.

9. Craig JM, Scott AL. Helminths in the lungs. Parasite Immunol. 2014; 36(9):463–74. https://doi.org/10.1111/pim.12102 PMID: 25201409.

10. Jukes MC, Nokes CA, Alcock KJ, Lambo JK, Kihamia C, Ngorosho N, et al. Heavy schistosomiasis associated with poor short-term memory and slower reaction times in Tanzanian schoolchildren. Trop Med Int Health. 2002; 7(2):104–17. Epub 2002/02/14. PMID: 11841700.

11. Albonico M, Allen H, Chitsulo L, Engels D, Gabrielli AF, Savioli L. Controlling soil-transmitted helminthiasis in pre-school-age children through preventive chemotherapy. PLoS Negl Trop Dis. 2008; 2(3):e126. Epub 2008/03/28. https://doi.org/10.1371/journal.pntd.0000126 PMID: 18365031; PubMed Central PMCID: PMCPMC2274864.

12. Scott SP, Chen-Edinboro LP, Caulfield LE, Murray-Kolb LE. The impact of anemia on child mortality: an updated review. Nutrients. 2014; 6(12):5915–32. Epub 2014/12/24. https://doi.org/10.3390/nu6125915 PMID: 25533005; PubMed Central PMCID: PMCPMC4277007.

13. Berhe N, Myrvang B, Gundersen SG. Gastro-intestinal symptoms associated with intense *Schistosoma mansoni* infection affect class-attentiveness of schoolchildren in Ethiopia. Acta Trop. 2009; 110(1):52–6. Epub 2009/03/14. PMID: 19283896.

14. DiNardo AR, Mace EM, Lesteberg K, Cirillo JD, Mandalakas AM, Graviss EA, et al. Schistosome soluble egg antigen decreases *Mycobacterium tuberculosis*-specific CD4+ T-Cell effector function with concomitant arrest of macrophage phago-lysosome maturation. J Infect Dis. 2016; 214(3):479–88. Epub 2016/07/09. https://doi.org/10.1093/infdis/jiw156 PMID: 27389351; PubMed Central PMCID: PMCPMC4936644.

15. Tristao-Sa R, Ribeiro-Rodrigues R, Johnson LT, Pereira FE, Dietze R. Intestinal nematodes and pulmonary tuberculosis. Rev Soc Bras Med Trop. 2002; 35(5):533–5. Epub 2003/03/08. PMID: 12621678.

16. Alemu A, Tegegne Y, Damte D, Melku M. *Schistosoma mansoni* and soil-transmitted helminths among preschool-aged children in Chuahit, Dembia district, Northwest Ethiopia: prevalence, intensity of infection and associated risk factors. BMC Public Health. 2016; 16:422. Epub 2016/05/25. https://doi.org/10.1186/s12889-016-2864-9 PMID: 27216255; PubMed Central PMCID: PMCPMC4876558.

17. Davis SM, Worrell CM, Wiegand RE, Odero KO, Suchdev PS, Ruth LJ, et al. Soil-transmitted helminths in pre-school-aged and school-aged children in an urban slum: a cross-sectional study of prevalence, distribution, and associated exposures. Am J Trop Med Hyg. 2014; 91(5):1002–10. https://doi.org/10.4269/ajtmh.14-0060 PMID: 25157123; PubMed Central PMCID: PMCPMC4228865.

18. WHO, Carter Centre. Intergrated control of the neglected tropical diseases: a neglected opportunity ripe for action. Paper jointly prepared by WHO and the Carter Center presented to the Global Health and the United Nations meeting, May 8, 2008. World Health Organization. 2008.

19. MoHSW. Strategic Master Plan for the Neglected Tropical Diseases Control Program 2017–2022 Tanzania Mainland. Ministry of Health and Social Welfare. 2017.

20. Colley DG, Binder S, Campbell C, King CH, Tchuem Tchuente LA, N'Goran EK, et al. A five-country evaluation of a point-of-care circulating cathodic antigen urine assay for the prevalence of *Schistosoma mansoni*. Am J Trop Med Hyg. 2013; 88(3):426–32. Epub 2013/01/23. https://doi.org/10.4269/ajtmh.12-0639 PMID: 23339198; PubMed Central PMCID: PMCPMC3592520.

21. MoHSW. Standard Treatment Guidelines and Essential Medicines List (4th Edition). 2013.

22. NTLP, MoHSW. National Guidelines for the Management of Tuberculosis in Children (1st edition). National Tuberculosis and Leprosy Programme and Ministry of Health and Social Welfare. 2012.

23. National Bureau of Statistics, Regional Commissioner's Office. Dar es Salaam Region Socio-economic Profile 2014 2014/11//.

24. Grimes DA, Schulz KF. Compared to what? Finding controls for case-control studies. Lancet. 2005; 365:1429–33. Epub 2005/04/20. https://doi.org/10.1016/S0140-6736(05)66379-9 PMID: 15836892.

25. Mandalakas AM, Kirchner HL, Lombard C, Walzl G, Grewal HM, Gie RP, et al. Well-quantified tuberculosis exposure is a reliable surrogate measure of tuberculosis infection. Int J Tuberc Lung Dis. 2012; 16(8):1033–9. Epub 2012/06/14. https://doi.org/10.5588/ijtld.12.0027 PMID: 22692027.

26. Salim N, Schindler T, Abdul U, Rothen J, Genton B, Lweno O, et al. Enterobiasis and strongyloidiasis and associated co-infections and morbidity markers in infants, preschool- and school-aged children from rural coastal Tanzania: a cross-sectional study. BMC Infect Dis. 2014; 14:644. Epub 2014/12/10. https://doi.org/10.1186/s12879-014-0644-7 PMID: 25486986; PubMed Central PMCID: PMCPMC4271451.

27. Gladstone M, Lancaster GA, Umar E, Nyirenda M, Kayira E, van den Broek NR, et al. The Malawi Developmental Assessment Tool (MDAT): the creation, validation, and reliability of a tool to assess child development in rural African settings. PLoS Med. 2010; 7(5):e1000273. Epub 2010/06/04. https://

doi.org/10.1371/journal.pmed.1000273 PMID: 20520849; PubMed Central PMCID: PMCPMC2876049.

28. McDonald CM, Manji KP, Kupka R, Bellinger DC, Spiegelman D, Kisenge R, et al. Stunting and wasting are associated with poorer psychomotor and mental development in HIV-exposed Tanzanian infants. J Nutr. 2013; 143(2):204–14. https://doi.org/10.3945/jn.112.168682 PMID: 23256148

29. Knopp S, Salim N, Schindler T, Karagiannis Voules DA, Rothen J, Lweno O, et al. Diagnostic accuracy of Kato-Katz, FLOTAC, Baermann, and PCR methods for the detection of light-intensity hookworm and *Strongyloides stercoralis* infections in Tanzania. Am J Trop Med Hyg. 2014; 90(3):535–45. Epub 2014/01/22. https://doi.org/10.4269/ajtmh.13-0268 PMID: 24445211; PubMed Central PMCID: PMCPMC3945701.

30. Ochodo EA, Gopalakrishna G, Spek B, Reitsma JB, van Lieshout L, Polman K, et al. Circulating antigen tests and urine reagent strips for diagnosis of active schistosomiasis in endemic areas. Cochrane Database Syst Rev. 2015;(3):CD009579. Epub 2015/03/12. https://doi.org/10.1002/14651858.CD009579.pub2 PMID: 25758180; PubMed Central PMCID: PMCPMC4455231.

31. Becker SL, Yap P, Horie NS, Alirol E, Barbe B, Bhatta NK, et al. Experiences and Lessons from a Multi-country NIDIAG study on persistent digestive disorders in the tropics. PLoS Negl Trop Dis. 2016; 10: e0004818. Epub 2016/11/05. https://doi.org/10.1371/journal.pntd.0004818 PMID: 27812101; PubMed Central PMCID: PMCPMC5094778.

32. WHO. Haemoglobin concenterations for the diagnosis of anaemia and assessment of severity World Health Organization. 2011.

33. WHO. The WHO Child Growth Standards World Health Organization. 2006.

34. Mazigo HD, Nuwaha F, Kinung'hi SM, Morona D, Pinot de Moira A, Wilson S, et al. Epidemiology and control of human schistosomiasis in Tanzania. Parasit Vectors. 2012; 5:274. Epub 2012/11/30. https://doi.org/10.1186/1756-3305-5-274 PMID: 23192005; PubMed Central PMCID: PMCPMC3549774.

35. Ruganuza DM, Mazigo HD, Waihenya R, Morona D, Mkoji GM. *Schistosoma mansoni* among pre-school children in Musozi village, Ukerewe Island, North-Western-Tanzania: prevalence and associated risk factors. Parasit Vectors. 2015; 8:377. Epub 2015/07/17. https://doi.org/10.1186/s13071-015-0997-9 PMID: 26178484; PubMed Central PMCID: PMCPMC4504164.

36. Mwakitalu ME, Malecela MN, Mosha FW, Simonsen PE. Urban schistosomiasis and soil transmitted helminthiases in young school children in Dar es Salaam and Tanga, Tanzania, after a decade of anthelminthic intervention. Acta Trop. 2014; 133:35–41. Epub 2014/02/06. https://doi.org/10.1016/j.actatropica.2014.01.012 PMID: 24495630.

37. Cabello RK, Beck LC, Massara CL, Murta FL, Guimaraes RJ, Pieri OS, et al. *Schistosoma mansoni* infection and related knowledge among schoolchildren in an endemic area of Minas Gerais, Brazil, prior to educational actions. Acta Trop. 2016; 164:208–15. Epub 2016/10/30. https://doi.org/10.1016/j.actatropica.2016.09.015 PMID: 27647573.

38. Matthys B, Tschannen AB, Tian-Bi NT, Comoé H, Diabaté S, Traoré M, et al. Risk factors for *Schistosoma mansoni* and hookworm in urban farming communities in western Côte d'Ivoire. Trop Med Int Health. 2007; 12:709–23. Epub 2007/06/07. https://doi.org/10.1111/j.1365-3156.2007.01841.x PMID: 17550468.

39. Olsen A, Kinung'hi S, Magnussen P. *Schistosoma mansoni* infection along the coast of Lake Victoria in Mwanza region, Tanzania. Am J Trop Med Hyg. 2015; 92(6):1240–4. Epub 2015/04/01. https://doi.org/10.4269/ajtmh.14-0676 PMID: 25825388; PubMed Central PMCID: PMCPMC4458831.

40. Sarda RK, Simonsen PE, Mahikwano LF. Urban transmission of urinary schistosomiasis in Dar es Salaam, Tanzania. Acta Trop. 1985; 42(1):71–8. Epub 1985/03/01. PMID: 2859753.

41. Brooker S, Clements AC. Spatial heterogeneity of parasite co-infection: Determinants and geostatistical prediction at regional scales. Int J Parasitol. 2009; 39(5):591–7. Epub 2008/12/17. https://doi.org/10.1016/j.ijpara.2008.10.014 PMID: 19073189; PubMed Central PMCID: PMCPMC2644303.

42. Yirgalem G/hiwot, Degarege A, Erko B. Prevalence of intestinal parasitic infections among children under five years of age with emphasis on *Schistosoma mansoni* in Wonji Shoa Sugar Estate, Ethiopia. PLoS One. 2014; 9(10):e109793. Epub 2014/10/09. https://doi.org/10.1371/journal.pone.0109793 PMID: 25296337; PubMed Central PMCID: PMCPMC4190315.

43. Kalison KD, Mwambete N. Prevalance of intestinal helminths infections among underfives and knowledge on helminthiases among mothers of the underfives in Dar es Salaam, Tanzania. East Afri J Public Health. 2006; 3:8–11.

44. Clarke NE, Clements AC, Doi SA, Wang D, Campbell SJ, Gray D, et al. Differential effect of mass deworming and targeted deworming for soil-transmitted helminth control in children: a systematic review and meta-analysis. Lancet. 2017; 389:287–97. Epub 2016/12/17. https://doi.org/10.1016/S0140-6736(16)32123-7 PMID: 27979381.

45. Worrell CM, Wiegand RE, Davis SM, Odero KO, Blackstock A, Cuéllar VM, et al. A Cross-sectional study of water, sanitation, and hygiene-related risk factors for soil-transmitted helminth infection in urban school- and preschool-aged children in Kibera, Nairobi. PLoS One. 2016; 11(3):e0150744. https://doi.org/10.1371/journal.pone.0150744 PMID: 26950552; PubMed Central PMCID: PMCPMC4780697.

46. Yimam Y, Degarege A, Erko B. Effect of anthelminthic treatment on helminth infection and related anaemia among school-age children in northwestern Ethiopia. BMC Infect Dis. 2016; 16(1):613. Epub 2016/10/30. https://doi.org/10.1186/s12879-016-1956-6 PMID: 27793110; PubMed Central PMCID: PMCPMC5084399.

47. Ministry of Health Community Development Gender Elderly and Children, Ministry of Health, National Bureau of Statistics, Office of the Chief Government Statistician, ICF. Tanzania Demographic and Health Survey and Malaria Indicator Survey (TDHS-MIS) 2015–16. 2016.

48. Erismann S, Knoblauch AM, Diagbouga S, Odermatt P, Gerold J, Shrestha A, et al. Prevalence and risk factors of undernutrition among schoolchildren in the Plateau Central and Centre-Ouest regions of Burkina Faso. Infect Dis Poverty. 2017; 6:17. Epub 2017/01/20. https://doi.org/10.1186/s40249-016-0230-x PMID: 28100278; PubMed Central PMCID: PMCPMC5244543.

49. Yentur Doni N, Yildiz Zeyrek F, Simsek Z, Gurses G, Sahin I. Risk factors and relationship between intestinal parasites and the growth retardation and psychomotor development delays of children in Sanliurfa, Turkey. Turkiye Parazitol Derg. 2015; 39(4):270–6. Epub 2016/01/27. https://doi.org/10.5152/tpd.2015.3620 PMID: 26809913.

50. Graham SM, Ahmed T, Amanullah F, Browning R, Cardenas V, Casenghi M, et al. Evaluation of tuberculosis diagnostics in children: 1. Proposed clinical case definitions for classification of intrathoracic tuberculosis disease. Consensus from an expert panel. J Infect Dis. 2012; 205 Suppl 2:S199–208. Epub 2012/03/27. https://doi.org/10.1093/infdis/jis008 PMID: 22448023; PubMed Central PMCID: PMCPMC3334506.

51. Zaman MM, Bhuiyan MR, Karim MN, MoniruzZaman, Rahman MM, Akanda AW, et al. Clustering of non-communicable diseases risk factors in Bangladeshi adults: An analysis of STEPS survey 2013. BMC Public Health. 2015; 15:659. Epub 2015/07/15. https://doi.org/10.1186/s12889-015-1938-4 PMID: 26169788; PubMed Central PMCID: PMCPMC4501055.

52. Andrews JR, Bogoch II, Utzinger J. The benefits of mass deworming on health outcomes: new evidence synthesis, the debate persists. The Lancet Global health. 2017; 5:e4–e5. Epub 2016/12/14. https://doi.org/10.1016/S2214-109X(16)30333-3 PMID: 27955787.