

# Prevalence of Intestinal Helminth Coinfection in Drug-Resistant Tuberculosis in Uganda

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**Background.** Although a third of people with tuberculosis (TB) are estimated to be coinfecting with helminths, the prevalence is largely unknown among people with drug-resistant TB (DR-TB). We determined the prevalence of helminth coinfection among people with DR-TB in Uganda.

**Methods.** In a multicenter, cross-sectional study, eligible Ugandan adults with confirmed DR-TB were consecutively enrolled between July to December 2021 at 4 treatment centers. Sociodemographic data were collected using a questionnaire. Participants underwent anthropometric and blood pressure measurements, and blood samples were evaluated for random blood glucose, glycated hemoglobin, nonfasting lipid profile, human immunodeficiency virus (HIV) infection, and a complete blood count. Fresh stool samples were evaluated for adult worms, eggs, and larvae using direct microscopy after Kato-Katz concentration techniques.

**Results.** Of 212 participants, 156 (73.6%) were male, 118 (55.7%) had HIV, and 3 (2.8%) had malaria coinfection. The prevalence of intestinal helminth coinfection was 4.7% (10/212) (95% confidence interval, 2.6%–8.6%). The frequency of helminth infections was *Ancylostoma duodenale* (n = 4), *Schistosoma mansoni* (n = 2), *Enterobius vermicularis* (n = 2), *Ascaris lumbricoides* (n = 1), and *Trichuris trichiura* (n = 1).

**Conclusions.** The prevalence of helminth coinfection was low among people with DR-TB. More studies are needed to determine the clinical relevance of helminth/DR-TB coinfection.

**Keywords.** DR-TB; drug-resistant tuberculosis; helminth; MDR; TB; worms.

Drug-resistant tuberculosis (DR-TB), which is the resistance of *Mycobacterium tuberculosis* (*Mtb*) to any first-line anti-tuberculosis (TB) agent, is a threat to TB control and accounts for >500 000 estimated TB cases worldwide [1]. DR-TB is associated with poor TB treatment outcomes, with a reported mortality rate of 21% in Africa [2]. The prevalence of multidrug-resistant TB in East Africa is 4% and 21% among new and previously treated people with TB, respectively [3]. In Uganda, the incidence of rifampicin-resistant TB has increased by 20% in the last 8 years, mostly among new TB cases [4].

About a third of people with TB are estimated to be coinfecting with soil-transmitted helminths (STHs), although the specific estimate for helminth/DR-TB coinfection is unknown [5]. Helminths cause immune activation of predominantly T-helper 2 (Th2) cells and down-regulation of both T-helper 1 (Th1) and cytotoxic T lymphocytes [6, 7]. This change in the immunological milieu of the host might impair the immunological response to *Mtb* complex, which needs Th1 responses to limit the severity and progression of infection [6]. In sub-Saharan Africa, where the prevalence of parasitic infections is very high (37%–48% [8, 9]), a dominant Th2 polarized immune response has been reported and suggested to increase susceptibility to *Mtb* [10].

As such, TB patients are twice as likely to be infested with intestinal helminths and are 2–3 times more likely to harbor ≥1 intestinal parasite compared to controls [11]. A more recent study has shown that parasitic coinfection is associated with more severe TB disease and high mycobacterial load [12]. It is unclear whether helminth coinfection is associated with severe DR-TB. Both intestinal helminthiasis and TB are endemic in Uganda [13, 14]. The prevalence of helminth infection

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among adults with drug-susceptible TB and DR-TB in Uganda is unknown. However, the prevalence of intestinal helminths is reported to be 54.8% among school children with variation in the prevalence for the specific helminths—*Ascaris lumbricoides* (6.3%), *Trichuris trichiura* (5.0%), and hookworm (43.5%) [15]. In this study, we determined the prevalence of intestinal helminth coinfection among people with DR-TB in Uganda.

## METHODS

### Study Design, Population, and Setting

We conducted a multicenter, cross-sectional study at 4 DR-TB treatment centers in Uganda. Uganda has 17 DR-TB treatment sites including 1 national referral, 14 regional referrals, and 2 district hospitals. One high-volume DR-TB treatment site was purposively selected from each of the 4 regions (Eastern, Northern, Western, and Central) of Uganda because high-risk water, sanitation, and hygiene practices are varied across these regions [16]. Specifically, participants were enrolled from Mulago, Mbarara, Lira, and Mbale referral hospitals. In this study, we included adults (aged  $\geq 18$  years) with bacteriologically confirmed TB, and a TB drug susceptibility test showing any form of drug resistance, who provided informed consent. We excluded people who reported a history of deworming in the preceding 2 weeks. We conducted a census of all people who were receiving treatment during the study period by consecutively enrolling them during the clinic appointment days at the study sites. The programmatic management of DR-TB in Uganda has been extensively described recently [17]. In brief, people were diagnosed with rifampicin-resistant TB using the *Mtb* Xpert/RIF assay. Baseline sputum samples were subsequently sent to the national TB reference laboratory for a full drug susceptibility test for resistance to isoniazid, rifampicin, fluoroquinolones, and second-line injectable aminoglycosides.

### Data Collection and Study Measurements

Research assistants underwent a 1-day training on the study tools and protocol. They administered a pretested questionnaire that collected sociodemographic characteristics, medical history, and any history of cigarette smoking and alcohol use from eligible participants. The study questionnaire was pretested among people with drug-susceptible TB at Mulago hospital. The study participants underwent measurement of their weight, height, and waist/hip ratio using a weighing scale (Seca 760), stadiometer (Seca 213), and tape measure, respectively. The body mass index (BMI) was calculated using the formula  $[BMI = \text{weight (kilograms)} / \text{height (meters)}^2]$ . Blood pressure (BP) measurements were performed using a battery-powered digital BP machine (Omron, Hem 7120) taken on 2 separate occasions, 20 minutes apart, at the DR-TB treatment center. The average BP of the 2 measurements was used as the participant's BP. A study nurse drew 4 mL of blood for

evaluation of the random blood glucose (RBG), glycated hemoglobin (HbA1c), nonfasting lipid profile, complete blood count, hemoparasites, and CD4 T-cell counts. The RBG was measured using a point-of-care glucometer (Accu-Chek). The HbA1c and blood lipids (triglycerides, total cholesterol, low-density lipoprotein cholesterol [LDL-c], and high-density lipoprotein cholesterol [HDL-c]) were estimated using the Cobas 6000 analyzer series (Roche Diagnostics). The complete blood count parameters were measured using a hem analyzer (Sysmex automated hematology analyzer XN 1000). A laboratory technologist prepared and examined thick blood smears for malaria parasites using a binocular microscope using 100 $\times$  objective according with standard procedures [18]. The CD4<sup>+</sup> T-cell counts were measured by flow cytometry (BD FACSCalibur) while human immunodeficiency virus (HIV) infection was confirmed using immunochromatographic tests according to the Uganda HIV testing guidelines [19]. Participants provided fresh stool samples on which we performed Kato-Katz concentration techniques [20]. A laboratory technologist examined stool samples for adult worms, eggs, and larvae by direct microscopy.

### Sample Size Estimation and Statistical Analysis

In Uganda, there were about 520 people receiving DR-TB treatment in 2021. Considering a prevalence of TB/STH coinfection of 31.5% [5], we estimated a sample size of 226 people with DR-TB to be adequate [21], considering a 95% confidence interval (CI) and a 10% possible withdrawal of consent. We therefore conducted a census of all people with DR-TB at the study sites to achieve the desired sample size. Data were entered in EpiData version 4.4.0 and exported to Stata version 16.0 for analysis. Continuous variables are presented as medians with the corresponding interquartile ranges (IQRs). Categorical data are presented as proportions. The prevalence of helminths/DR-TB coinfection was calculated as the proportion of people with at least 1 of the infections to the total number of people with DR-TB. People with and without helminth infection were compared using Pearson  $\chi^2$  (or Fisher exact) test and Mann-Whitney *U* test for categorical and continuous variables, respectively. We used logistic regression to determine factors independently associated with helminth coinfection. In constructing a multivariable logistic regression model, all factors with  $P < .2$  in bivariable analysis for factors associated with helminth coinfection were entered in the final model as is conventionally recommended [22]. A  $P$  value  $< .05$  was considered statistically significant.

## RESULTS

We screened 222 participants, of whom 212 (95.5%) were enrolled and 10 were excluded. Of those excluded, 4 were aged

**Table 1. Characteristics of Study Participants**

| Characteristic                                    | Overall (N = 212) | Helminth Coinfection (n = 10) | Without Helminth Coinfection (n = 202) | P Value           |
|---|-------------------|-------------------------------|--|-------------------|
| <b>Study site</b>                                 |                   |                               |  | .148              |
| Lira (northern Uganda)                            | 85 (40.1)         | 6 (60)                        | 79 (39.1)                              |                   |
| Mulago (central Uganda)                           | 83 (39.2)         | 1 (10)                        | 82 (40.6)                              |                   |
| Mbale (eastern Uganda)                            | 25 (11.8)         | 2 (20)                        | 23 (11.4)                              |                   |
| Mbarara (western Uganda)                          | 19 (9)            | 1 (10)                        | 18 (8.9)                               |                   |
| <b>Residence</b>                                  |                   |                               |  | .093              |
| Rural   | 128 (60.4)        | 9 (90)                        | 119 (58.9)                             |                   |
| Urban   | 84 (39.6)         | 1 (10)                        | 83 (41.1)                              |                   |
| <b>Marital status</b>                             |                   |                               |  |                   |
| Married   | 112 (52.8)        | 7 (70)                        | 105 (52)                               | .875              |
| Never married                                     | 26 (12.3)         | 1 (10)                        | 25 (12.4)                              |                   |
| Divorced or separated                             | 65 (30.7)         | 2 (20)                        | 63 (31.2)                              |                   |
| Widowed   | 9 (4.2)           | 0 (0)                         | 9 (4.5)                                |                   |
| <b>Education level</b>                            |                   |                               |  | .690              |
| None  | 18 (8.5)          | 0 (0)                         | 18 (9)                                 |                   |
| Primary school                                    | 122 (57.8)        | 8 (80)                        | 114 (56.7)                             |                   |
| Secondary school                                  | 55 (26.1)         | 2 (20)                        | 53 (26.4)                              |                   |
| Tertiary/university                               | 16 (7.6)          | 0 (0)                         | 16 (8)                                 |                   |
| <b>Employment</b>                                 |                   |                               |  | .663              |
| Peasant farmer                                    | 92 (43.4)         | 5 (50)                        | 87 (43.1)                              |                   |
| Self-employed                                     | 48 (22.6)         | 1 (10)                        | 47 (23.3)                              |                   |
| Unemployed  | 38 (17.9)         | 3 (30)                        | 35 (17.3)                              |                   |
| Formal employment                                 | 34 (16)           | 1 (10)                        | 33 (16.3)                              |                   |
| <b>Symptoms</b>                                   |                   |                               |  |                   |
| Abdominal discomfort                              | 106 (50)          | 3 (30)                        | 103 (51)                               | .195              |
| Blood in urine                                    | 11 (5.2)          | 0 (0)                         | 11 (5.4)                               | .580              |
| Night sweats                                      | 115 (54.2)        | 6 (60)                        | 109 (54)                               | .757              |
| Chest pain  | 121 (57.1)        | 6 (60)                        | 115 (56.9)                             | .559              |
| Cough   | 130 (61.3)        | 8 (80)                        | 122 (60.4)                             | .323              |
| Hemoptysis  | 15 (7.1)          | 2 (20)                        | 13 (6.4)                               | .151              |
| Blood in stool                                    | 28 (13.2)         | 1 (10)                        | 27 (13.4)                              | .610              |
| Anorexia  | 40 (18.9)         | 2 (20)                        | 38 (18.8)                              | .594              |
| Diarrhea  | 43 (20.3)         | 5 (50)                        | 38 (18.8)                              | .031 <sup>a</sup> |
| Dyspnea   | 63 (29.7)         | 4 (40)                        | 59 (29.2)                              | .488              |
| Skin rash   | 70 (33)           | 4 (40)                        | 66 (32.7)                              | .733              |
| Nausea  | 79 (37.3)         | 4 (40)                        | 75 (37.1)                              | .549              |
| Constipation                                      | 95 (44.8)         | 4 (40)                        | 91 (45)                                | .509              |
| <b>Type of DR-TB at baseline (n = 210)</b>        |                   |                               |  | .989              |
| RR-TB/MDR-TB                                      | 204 (97.1)        | 10 (100)                      | 194 (97)                               |                   |
| Polyresistant TB                                  | 1 (0.5)           | 0 (0)                         | 1 (0.5)                                |                   |
| Pre-XDR-TB  | 3 (1.4)           | 0 (0)                         | 3 (1.5)                                |                   |
| XDR-TB  | 1 (0.5)           | 0 (0)                         | 1 (0.5)                                |                   |
| Monoresistant TB                                  | 1 (0.5)           | 0 (0)                         | 1 (0.5)                                |                   |
| <b>Previous TB episode (n = 211)</b>              |                   |                               |  | .750              |
| 110 (52.1)  | 6 (60)            | 104 (51.7)                    |  |                   |
| <b>Mtb load at baseline<sup>b</sup> (n = 170)</b> |                   |                               |  | .227              |
| High  | 52 (30.6)         | 3 (30)                        | 49 (30.6)                              |                   |
| Medium  | 35 (20.6)         | 1 (10)                        | 34 (21.3)                              |                   |

**Table 1. Continued**

| Characteristic   | Overall (N = 212) | Helminth Coinfection (n = 10) | Without Helminth Coinfection (n = 202) | P Value |
|--|-------------------|-------------------------------|--|---------|
| Low  | 28 (16.5)         | 4 (40)                        | 24 (15)                                |         |
| Very low   | 55 (32.4)         | 2 (20)                        | 53 (33.1)                              |         |
| <b>Drugs in the treatment regimen (n = 209)</b>                |                   |                               |  |         |
| Ethionamide  | 10 (4.8)          | 0 (0)                         | 10 (5)                                 | .606    |
| Pyrazinamide   | 39 (18.7)         | 0 (0)                         | 39 (19.6)                              | .214    |
| Cycloserine  | 197 (94.3)        | 9 (90)                        | 188 (94.5)                             | .454    |
| Levofloxacin   | 200 (95.7)        | 10 (100)                      | 190 (95.5)                             | .638    |
| Ethambutol   | 6 (2.9)           | 1 (10)                        | 5 (2.5)                                | .258    |
| Clofazimine  | 197 (94.3)        | 10 (100)                      | 187 (94)                               | .546    |
| Moxifloxacin   | 2 (1)             | 0 (0)                         | 2 (1)                                  | .906    |
| Bedaquiline  | 157 (75.1)        | 9 (90)                        | 148 (74.4)                             | .457    |
| Linezolid  | 165 (78.9)        | 10 (100)                      | 155 (77.9)                             | .125    |
| Amikacin   | 1 (0.5)           | 0 (0)                         | 1 (0.5)                                | .952    |
| Delamanid  | 8 (3.8)           | 0 (0)                         | 8 (4)                                  | .671    |
| <b>Time to treatment initiation, d, median (IQR) (n = 202)</b> | 8 (5–14)          | 9.5 (4–13)                    | 8 (5–14.5)                             | .496    |

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: DR-TB, drug-resistant tuberculosis; IQR, interquartile range; MDR-TB, multidrug-resistant tuberculosis; *Mtb*, *Mycobacterium tuberculosis*; RR-TB, rifampicin-resistant tuberculosis; TB, tuberculosis; XDR-TB, extensively drug-resistant tuberculosis.

<sup>a</sup>Statistically significant result.

<sup>b</sup>Determined by cycle threshold values of the Xpert MTB/RIF assay.

<18 years, 4 failed to provide a stool sample, and 2 withdrew consent.

**Characteristics of Study Participants**

Of 212 participants, 156 (73.6%) were male (Table 1). At enrollment in the study, the median month of DR-TB treatment was month 8 (IQR, 4–13). Overall, 97 (46.0%) reported a history of deworming. The median age was 37 (IQR, 30–46) years (n = 211). Overall, 148 (69.8%) reported a history of alcohol use and 77 (36.3%) reported a history of smoking. Among the participants, 118 (55.7%) had HIV coinfection, 4 (1.9%) had hypertension, and 3 (1.4%) had diabetes mellitus. The median BMI was 19.7 (IQR, 17.7–22.2) kg/m<sup>2</sup> (n = 199) while the systolic and diastolic BPs were 124.0 (IQR, 116.0–133.5) mm Hg and 85.3 (IQR, 76.5–93.0) mm Hg, respectively.

Among the participants, the median hemoglobin level was 14.5 (IQR, 12.4–16.2) g/dL (n = 187), the lymphocyte count was 1200 (IQR, 270–1700) cells/μL, the eosinophil count was 240 (IQR, 70–640) cells/μL (n = 163), and the CD4<sup>+</sup> T-cell count (n = 130) was 439 (IQR, 247–643) cells/μL. Three of 107 participants (2.8%) had malaria coinfection. The median RBG was 4.6 (IQR, 4.0–5.7) mmol/L and the median HbA1c was 4.7% (IQR, 3.9%–5.2%). Regarding the blood lipids, the median values were as follows: total cholesterol, 3.4 (IQR,

**Table 2. Frequency of Water, Sanitation, and Hygiene Practices Among People With Drug-Resistant Tuberculosis**

| Characteristic                            | Overall (N = 212) | Helminth Coinfection (n = 10) | Without Helminth Coinfection (n = 202) | P Value           |
|---|-------------------|-------------------------------|--|-------------------|
| Source of food                            |                   |                               |  | .650              |
| Mostly cooks own food                     | 180 (84.9)        | 8 (80)                        | 172 (85.1)                             |                   |
| Mostly eats at restaurant or hotel        | 32 (15.1)         | 2 (20)                        | 30 (14.9)                              |                   |
| Eats raw meat                             | 130 (61.3)        | 7 (70)                        | 123 (60.9)                             | .744              |
| Source of drinking water                  |                   |                               |  |                   |
| Tap or pipe                               | 83 (39.2)         | 2 (20)                        | 81 (40.1)                              | .396              |
| Open well or river                        | 47 (22.2)         | 2 (20)                        | 45 (22.3)                              |                   |
| Borehole                                  | 74 (34.9)         | 6 (60)                        | 68 (33.7)                              |                   |
| Other                                     | 8 (3.8)           | 0 (0)                         | 8 (4)                                  |                   |
| Swims in freshwater bodies                | 103 (48.6)        | 7 (70)                        | 96 (47.5)                              | .205              |
| Has pets at home                          | 83 (39.2)         | 3 (30)                        | 80 (39.6)                              | .074              |
| Rears cattle                              | 125 (59)          | 7 (70)                        | 118 (58.4)                             | .531              |
| Rears poultry                             | 146 (68.9)        | 10 (100)                      | 136 (67.3)                             | .033 <sup>a</sup> |
| Wears shoes                               |                   |                               |  | .791              |
| Always wears shoes                        | 134 (63.2)        | 6 (60)                        | 128 (63.4)                             |                   |
| Occasionally                              | 74 (34.9)         | 4 (40)                        | 70 (34.7)                              |                   |
| Never wears                               | 4 (1.9)           | 0 (0)                         | 4 (2)                                  |                   |
| Participates in fishing activities        | 71 (33.5)         | 5 (50)                        | 66 (32.7)                              | .308              |
| History of deworming                      | 97 (46)           | 5 (50)                        | 92 (45.8)                              | .522              |
| Always washes hands before eating food    | 194 (91.5)        | 10 (100)                      | 184 (91.1)                             | .403              |
| Always washes hands before preparing food | 97 (45.8)         | 7 (70)                        | 90 (44.6)                              | .192              |
| Has toilet or latrine at home             | 203 (95.8)        | 9 (90)                        | 194 (96)                               | .358              |
| Labors barefoot in garden or farmland     | 87 (41)           | 6 (60)                        | 81 (40.1)                              | .324              |

Data are presented as No. (%) unless otherwise indicated.

<sup>a</sup>Statistically significant result.

2.7–4.2) mmol/L; LDL-c, 1.7 (IQR, 1.2–2.2) mmol/L; HDL-c, 1.2 (IQR, 0.9–1.7) mmol/L; and triglycerides, 1.2 (IQR, 0.87–1.62) mmol/L. Other characteristics are shown in [Tables 1 and 2](#). The [Supplementary Material](#) compares blood measurements among people with and without helminth coinfection.

#### Prevalence of Helminth Coinfection Among People With DR-TB in Uganda

The prevalence of helminth coinfection was 4.7% (10/212) (95% CI, 2.6%–8.6%). The frequency of helminth infections was as follows: *Ancylostoma duodenale* (n = 4), *Schistosoma mansoni* (n = 2), *Enterobius vermicularis* (n = 2), *A lumbricoides* (n = 1), and *T trichiura* (n = 1). People with helminth infection had higher median lymphocyte counts than those without (1770 vs 1110 cells/ $\mu$ L;  $P = .049$ ). Furthermore, the median triglyceride level (1.4 vs 1.2 mmol/L,  $P = .048$ ) was higher among people with helminth coinfection than those without, respectively (see figures in [Supplementary Material](#)).

#### Factors Associated With Helminth Infection

In our bivariable analyses, diarrhea (odds ratio [OR], 4.32 [95% CI, 1.19–15.66]) was significantly associated with helminth infection. Additionally, all people with helminth coinfection raised poultry (100% vs 67.3%,  $P = .033$ ). Other variables, including a history of deworming >2 weeks before enrollment (OR, 1.18 [95% CI, .33–4.22]) and HIV coinfection (OR, 0.51

[95% CI, .14–1.88]), were not associated with helminth infection. In our multivariable analysis, helminth infection was only associated with an increase in the diastolic BP (adjusted OR, 1.12 [95% CI, 1.01–1.24]) ([Table 3](#)).

## DISCUSSION

In this study, we determined the prevalence of helminth infection among people with DR-TB. We found a low prevalence of helminth infection of about 5%. The organisms identified were *A duodenale*, *S mansoni*, *E vermicularis*, *A lumbricoides*, and *T trichiura*. Incidentally, we also found a low prevalence of malaria, a hemoparasite. To our knowledge, this is the first study to evaluate the prevalence of helminth infection in people with DR-TB. The study therefore fills a knowledge gap. A low prevalence of intestinal parasites was also reported in Ethiopia (2%), Iran (2%), and China (7%) among people with pulmonary TB, although TB drug susceptibility testing was not performed [23–25]. Our estimate is lower than the prevalence reported in systematic reviews of studies among people with predominantly susceptible TB (26%–32%) [5, 26]. It is not apparent why we found a low prevalence of helminth coinfection. However, the low prevalence in our study could be due to the high rate of previous deworming observed among 46% of our participants; although there were no people who had been dewormed

**Table 3. Multivariable Analysis for Factors Associated With Helminth Infection Among People With Drug-Resistant Tuberculosis**

| Variable                                  | OR (95% CI)       | P Value | Adjusted OR (95% CI) | P Value |
|---|-------------------|---------|----------------------|---------|
| <b>Diarrhea</b>                           |                   |         |                      |         |
| No  | Reference         |         | Reference            |         |
| Yes                                       | 4.32 (1.19–15.66) | .026    | 5.33 (.53–53.61)     | .155    |
| Triglycerides                             | 1.81 (.84–3.91)   | .129    | 2.39 (.71–8.00)      | .158    |
| HDL-c                                     | 2.07 (.95–4.50)   | .067    | 0.73 (.13–4.18)      | .725    |
| LDL-c                                     | 1.41 (.99–1.99)   | .055    | 1.69 (.71–4.02)      | .234    |
| Diastolic BP                              | 1.04 (.99–1.09)   | .166    | 1.12 (1.01–1.24)     | .039    |
| Hemoglobin                                | 1.18 (.96–1.46)   | .123    | 1.29 (.85–1.98)      | .232    |
| Lymphocytes                               | 1.94 (.91–4.11)   | .084    | 2.40 (.64–9.03)      | .196    |
| Mid-upper arm circumference               | 1.13 (.939–1.368) | .193    | 1.12 (.79–1.57)      | .535    |
| <b>Previous TB episode</b>                |                   |         |                      |         |
| No  | Reference         |         | Reference            |         |
| Yes                                       | 3.69 (.77–17.82)  | .104    | 8.17 (.75–89.02)     | .085    |
| <b>Washes hands before preparing food</b> |                   |         |                      |         |
| No  | Reference         |         | Reference            |         |
| Yes                                       | 2.90 (.73–11.55)  | .130    | 15.38 (.99–238.45)   | .051    |
| <b>Swimming in freshwater bodies</b>      |                   |         |                      |         |
| No  | Reference         |         | Reference            |         |
| Yes                                       | 2.58 (.65–10.25)  | .179    | 3.13 (.37–26.56)     | .295    |
| <b>Residence</b>                          |                   |         |                      |         |
| Urban                                     | Reference         |         | Reference            |         |
| Rural                                     | 6.27 (.78–50.49)  | .084    | 1.36 (.06–30.04)     | .845    |

Abbreviations: BP, blood pressure; CI, confidence interval; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; OR, odds ratio; TB, tuberculosis.

in the preceding 2 weeks. Nonetheless, deworming was not associated with helminth coinfection in our study. Moreover, high rates of previous use of anthelmintic medicine are reported in rural and urban Uganda, but this does not seem to affect the prevalence of helminth infection significantly [27]. There is also the possibility that community-wide de-worming campaigns and improvements in sanitation levels over the years have reduced the burden of intestinal parasites in Uganda [28]. Another possible explanation is that participants in our study had been substantially exposed (median of 8 months) to anti-TB treatment, which may have antiparasitic effects. Clofazimine is active against *Schistosoma* spp for which it reduces the worm burden by >80% [29]. Further, linezolid and its analogues have antiparasitic activity against the *Hymenolepis nana* tapeworm [30]. These agents are part of the second-line agents used in Uganda and were in the TB regimens of >70% our participants. More studies are needed to establish the burden of helminth infection among people with DR-TB and whether this is higher before treatment initiation than during DR-TB treatment. The prevalence of malaria in our study (2.8%) is similar to that reported at a national TB treatment center in Uganda (2.2%) [31] but the clinical relevance of TB/malaria coinfection is unclear. The effect of TB/malaria coinfection on the clinical presentation and treatment outcome of either disease needs to be investigated further.

The associations of helminth coinfection in our study should be interpreted with caution because of the low prevalence. Our study found higher triglyceride levels in people with helminth

coinfection. Moreover, there was a trend toward higher HDL-c and LDL-c levels among people with helminths at bivariate analysis. This was surprising because studies suggest that helminth infection is associated with low triglyceride levels (and indeed other lipid parameters) in the general population [32, 33]. However, one must be careful not to infer observations in the general population to people with active TB. Lipid metabolism and disorders in TB are not well characterized in literature. Hyperlipidemia may be associated with an increased risk of active TB [34]. In support of this, a recent meta-analysis has shown that statins reduce the risk of active TB and *Mtb* in host immune cells [35]. *Mtb* also causes dysregulation in host lipid metabolism to facilitate its survival in the granuloma [36]. It does this by upregulating the expression of peroxisome proliferator-activated receptors (PPAR- $\gamma$ ) and CD36, a low-density lipoprotein receptor, to increase cellular uptake and accumulation of lipids in the infected cells [37]. The bacilli can then utilize the host's cholesterol as a source of energy and carbon [38]. This could explain why people with TB have lower serum levels of total cholesterol, triglycerides, LDL-c, and HDL-c than normal controls [39]. Expectedly, these levels tend to increase to above baseline levels after anti-TB therapy [40]. It is unclear whether helminths affect the lipid metabolism of *Mtb*. Helminths are also known to reduce blood lipids by utilization of the host's nutrients, altering intestinal microbiota and lipid metabolism in immune cells [33]. The effect of helminth coinfection on the lipid metabolism of *Mtb* and how this interaction affects lipid serum levels deserves further investigation.

People with helminth coinfection in our study had higher lymphocyte counts than those without. Evidently, these were not CD4<sup>+</sup> T lymphocytes because a comparison of these showed no statistically significant difference. It is therefore likely that these were predominantly CD8<sup>+</sup> T lymphocytes, although these were not measured. CD8<sup>+</sup> T lymphocytes play a central role in the pathophysiology of hypertension [41]. These cells infiltrate the renal interstitium and vasculature, resulting in vascular rarefaction and activation of the renin-angiotensin pathway that ultimately results in salt and volume expansion [42]. Further, the mineralocorticoid receptor on CD8<sup>+</sup> T cells interacts with the nuclear factor of activated T cells-1 and activator protein-1 to potentiate the production of prohypertension cytokines [43]. Additionally, CD8<sup>+</sup> T cells contact the distal convoluted tubules in the kidney where they up-regulate the sodium/chloride co-transporter to cause salt-sensitive hypertension [44]. We therefore hypothesize that the high lymphocytes (presumably CD8<sup>+</sup> T lymphocytes) among people with helminth coinfection in our study could explain why helminth coinfection was associated with elevated diastolic pressure. However, this deserves further evaluation. Elevated BP in TB has recently been associated with poor TB outcomes [45].

The key finding from our study is the low prevalence of intestinal helminths among people with DR-TB. The clinical implication of helminth eradication treatments/strategies in DR-TB is not apparent and is an area for further research. We used a multicenter approach, and this makes our findings somewhat generalizable in similar settings. Nevertheless, there are some limitations. First, the number of people with helminth coinfection were relatively few. This could have affected the study power to detect important differences among people with and without helminth coinfection. Furthermore, some water, sanitation, and hygiene practices and history of deworming can be affected by recall bias. Last, we used different equipment to measure anthropometrics and BP at the different study sites. This could introduce measurement bias. However, all equipment were of the same make/brand.

## CONCLUSIONS

The prevalence of intestinal helminths was low in people with DR-TB. Hookworm was the predominant helminth identified. However, helminth coinfection may elevate triglyceride levels and diastolic BP in this population, but this needs to be ascertained by larger studies. Studies are also needed to determine the clinical utility of helminth eradication strategies/therapies in DR-TB.

## Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the

authors, so questions or comments should be addressed to the corresponding author.

## Notes

**Author contributions.** J. B. B.: Conceptualization, methodology, investigation, data accrual, formal analysis, interpretation of results, drafting manuscript, revision of manuscript, final approval. M. N.: Methodology, formal analysis, interpretation of results, revision of manuscript, final approval. B. N. and D. W.: Data accrual, interpretation of results, revision of manuscript, final approval. A. W., J. N., S. N., R. K., E. N., and M. O.: Investigation, data accrual, interpretation of results, revision of manuscript, final approval. F. B. and I. A.-B.: Conceptualization, methodology, investigation, interpretation of results, revision of manuscript, final approval. K. N.: Investigation, interpretation of results, revision of manuscript, final approval. P. K. and C. S.: Conceptualization, interpretation of results, revision of manuscript, final approval.

**Patient consent.** All methods were performed in accordance with the relevant guidelines and regulations. Participants provided written informed consent to participate in the study. The study was approved by the Mulago Hospital Research and Ethics Committee (MHREC-2020-23), and the Uganda National Council of Science and Technology (HS1521ES) prior to participant recruitment.

**Data availability.** The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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