The extent, nature, and pathogenic consequences of helminth polyparasitism in humans: A meta-analysis

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Abstract

Background

Individual helminth infections are ubiquitous in the tropics; geographical overlaps in endemcity and epidemiological reports suggest areas endemic for multiple helminthiases are also burdened with high prevalences of intestinal protozoan infections, malaria, tuberculosis (TB), and human immunodeficiency virus (HIV). Despite this, pathogens tend to be studied in isolation, and there remains a need for a better understanding of the community ecology and health consequences of helminth polyparasitism to inform the design of effective parasite control programs.

Methodology

We performed meta-analyses to (i) evaluate the commonality of polyparasitism for helminth-helminth, helminth-intestinal protozoa, helminth-malaria, helminth-TB, and helminth-HIV co-infections, (ii) assess the potential for interspecies interactions among helminth-helminth and helminth-intestinal protozoan infections, and (iii) determine the presence and magnitude of association between specific parasite pairs. Additionally, we conducted a review of reported health consequences of multiply-infected individuals compared to singly- or not multiply-infected individuals.

Principal findings

We found that helminth-helminth and helminth-intestinal protozoan multiple infections were significantly more common than single infections, while individuals with malaria, TB, and HIV were more likely to be singly-infected with these infections than co-infected with at least one helminth. Most observed species density distributions significantly differed from the expected distributions, suggesting the potential presence of interspecies interactions. All significant associations between parasite pairs were positive in direction, irrespective of the combination of pathogens. Polyparasitized individuals largely exhibited lower hemoglobin levels and higher anemia prevalence, while the differences in growth-related variables were mostly statistically insignificant.
Conclusions

Our findings confirm that helminth polyparasitism and co-infection with major diseases is common in the tropics. A multitude of factors acting at various hierarchical levels, such as interspecies interactions at the within-host infra-parasite community level and environmental variables at the higher host community level, could explain the observed positive associations between pathogens; there remains a need to develop new frameworks which can consider these multilevel factors to better understand the processes structuring parasite communities to accomplish their control.

Author summary

Helminth infections are a highly prevalent global health problem. These parasitic worm infections occur in areas also burdened with intestinal protozoan infections, malaria, tuberculosis, and human immunodeficiency virus. While these pathogens tend to be studied in isolation, there remains a need to better understand the nature, extent, and health consequences of helminth polyparasitism and co-infection with major diseases. Here, we reviewed the literature and performed meta-analyses to evaluate the commonality of helminth polyparasitism and co-infection, the potential for interspecies interactions between parasites, the association between parasite pairs, and the health consequences among multiply-infected individuals. We confirmed that polyparasitism and co-infection with major diseases are common in the global South and found that multiply-infected individuals experienced worse health consequences when compared to singly or not-multiply infected individuals. Our analysis suggested the potential presence of interspecies interactions and we identified the existence of positive associations between parasite pairs. These findings support the call for integrating deworming into malaria, TB, and HIV treatment protocols and suggest there remains a need to improve our understanding of the factors influencing co-transmission to achieve sustainable parasite control.

Introduction

Helminth infections continue to be ubiquitous in the tropics with the 2016 Global Burden of Disease study indicating that currently 800 million individuals are likely to be infected worldwide with *A. lumbricoides*, 451 million with hookworm, 435 million with *T. trichiura*, and 190 million with schistosomiasis [1]. These figures suggest that worm infections may continue to induce significant morbidity on the world’s poorest populations; indeed, the latest 2016 disability-adjusted life year (DALY) estimates suggest that infection by these parasites could contribute to a loss of 6.6 million years lived with disability (YLD) presently, representing up to 6.5% of all the YLD due to communicable, maternal, neonatal, and nutritional diseases globally [1].

It has long been recognized that polyparasitism with helminths is a common feature of human infections in helminth-endemic regions. Areas endemic for multiple helminthiases have been shown to also harbor a higher burden of intestinal protozoan infections, malaria, tuberculosis (TB), and human immunodeficiency virus (HIV) [2]. Geographic patterns in endemicity, for example, have demonstrated that helminth co-infection with TB and HIV are pervasive in tropical geographies [2], and a recent meta-analysis indicated that soil-transmitted helminths and malaria may also be similarly co-endemic [3]. The transmission dynamics of
these infections are influenced by polyparasitic infections; infection by one parasite species can alter host susceptibility to additional parasite species [4]. There is growing literature demonstrating that helminth infections can detrimentally reduce host resistance to the microbes causing TB, HIV, and malaria [5]. Additionally, helminth infections have been found to affect vaccine efficacy [6], which may also influence the occurrence of these major co-infections. For example, studies have found that helminths hinder the immune response to the oral cholera vaccine [7] and similarly that helminth-infected individuals have impaired immune responses to vaccines for tuberculosis and tetanus compared to non-helminth-infected individuals [8–12].

These results, coupled with insights from studies of infectious disease transmission taking a community ecology perspective [13,14], suggest that helminth infections may continue to persist in the world’s poorest communities in spite of the enactment of large-scale national control programs. Indeed, increasing research has also demonstrated how interventions focused on one species alone in such a complex could result in unintended and potentially perverse health consequences resulting from the remaining infections [15–17]. These results indicate that gaining a better understanding of the extent and community ecology of helminth polyparasitism is a major need if effective control of these widespread and persistent infections is to be achieved [13,14,18,19]. In spite of these findings, parasites, including helminths, tend still to be studied in isolation, presumably because of the diagnostic challenges of undertaking multiple infection studies [20,21].

Despite the commonality and potential importance of helminth polyparasitism, the health consequences are not well-studied [20–23], likely due to the diagnostic challenges as well as the non-specific morbidity and chronic nature of helminth infections [20,24]. A 2008 review of existing studies on the health implications of soil-transmitted helminths, schistosomiasis, and malaria indicates that polyparasitism may have an additive and/or synergistic effect on nutrition and organ pathology [22]. An additional review of the literature related to all co-infections published in 2009 also found co-infections to be associated with larger negative health effects [23]. These studies indicate that by examining diseases individually, the true human health burden induced by the polyparasitic nature of helminth infections could be seriously underestimated [22,23].

The above indicates that quantifying the fundamental patterns of helminth polyparasitism, including the relative frequency of co-infection with various major pathogens and infection/morbidity differences between single-species and co-infection, will constitute a first step in assessing the potential impact that polyparasitism can play not only in shaping observed parasitic infection prevalences and pathology, but also for improving prospects for achieving effective parasite control in endemic communities [13].

Here, we report on a survey and analysis of the published data on helminth polyparasitism to address these questions. We performed a meta-analysis of the assembled data following PRISMA guidelines [25] to evaluate the frequency of helminth co-infections and the presence and magnitude of the observed interspecific associations between specific parasite pairs; whereas we conducted a review together with a vote-counting-based analysis of compiled studies to evaluate the morbidity outcomes associated with each specific helminth polyparasitism type.

**Methods**

**Meta-analysis framework**

We collected and synthesized information from three different types of data: Type I (single and multiple infection prevalence data), Type II (frequency of individuals infected with 0, 1, 2, . . . , N parasite species), and Type III (association data).
Search strategy and selection criteria

We searched the PubMed and Web of Science databases for studies published from inception to March 2017. We developed a search strategy using the following MeSH terms and keywords: “polyparasitism” AND “human”, “helminth” AND “malaria” OR “tuberculosis” OR “HIV”, “helminth” AND “coinfection” AND “human”, and “parasitic” AND “coinfection” AND “human.” We also identified additional references from the bibliographies of included studies.

Overall, study inclusion criteria are as follows: 1) study written in English, 2) study assessed human populations, 3) study included both sexes, and 4) standard diagnostic measures for helminths and the investigated co-infections were met. For tuberculosis, we excluded studies using the TB skin test due to the possibility of obtaining a false positive test from the Bacillus Calmette–Guérin vaccine. Due to the different objectives for each study type, specific inclusion and exclusion criteria for the different types of data are listed below.

Type I data evaluated the difference between single and multiple infection prevalence for helminth-helminth, helminth-intestinal protozoa, and helminth-malaria at the community level. To most accurately gain insight into the prevalence of co-infections that would be found in a community rather than a subset of the population, the relevant studies here had to meet the following criteria: 1) community- or school-based cross-sectional study design, 2) single and multiple co-infection data available for extraction, and 3) analysis of at least three helminth species for helminth-only, and two helminths for helminth-intestinal protozoa and helminth-malaria investigations.

Due to a paucity of community-based studies for helminth-HIV and helminth-TB studies, we assessed the mean difference of helminth-co-infected and HIV or TB singly infected individuals, respectively. This allowed the inclusion of additional study designs as well as studies conducted on subsets of the population. Inclusion criteria for these studies included: 1) case-control, cross-sectional, cohort or baseline randomized controlled trial study design, 2) provision of helminth prevalence among infected individuals, and 3) examination of at least two helminths. Studies were excluded if they focused on individuals presenting with diarrheal symptoms.

The Type II analysis evaluated the potential for interspecies interactions by comparing the observed species density frequency distributions to those expected assuming parasitic infection events are independent. Type II data used the same selection criteria as Type I, except that the Type II data required the number of individuals infected with 0, 1, 2, . . ., N parasites and the prevalence of each individual parasite in the study community.

Type III studies providing association data had to meet the following criteria: 1) case-control, cross-sectional, cohort, or randomized controlled trial study design; 2) evaluation of associations between specific parasite pairs; and 3) provision of crude odds ratio, adjusted odds ratio, and/or data available to construct a 2x2 contingency table.

Identified titles and abstracts were examined by two independent reviewers (ZKC and RED). The full texts of potentially relevant articles were also evaluated by the same two reviewers. Articles meeting the inclusion criteria for the meta-analysis were subsequently screened for inclusion in the review of morbidity outcomes associated with polyparasitism.

Meta-analysis methods

For Type I studies that provided single and multiple infection prevalence data, we generated corrected mean difference values, weighting for sample size using the correction statistic J as presented by Poulin [26]:

$$J = 1 - \frac{3}{4(N_s + N_m - 2) - 1}$$
The J values were then used to calculate the corrected mean difference (\(d\)) values:

\[
d = J \left( \frac{\text{crude mean difference, multiple} - \text{single}}{100} \right)
\]

Note, here for helminth-intestinal protozoa studies, we simply compared multiple versus single infection prevalences, irrespective of whether single infections were due to helminth or protozoan infection only. By contrast, for helminth-malaria, helminth-HIV, and helminth-TB, given the lack of information regarding single helminth infections, we compared the prevalence of helminth-malaria, helminth-HIV, and helminth-TB co-infected against malaria, HIV, and TB infection only, respectively.

For Type I helminth-malaria, helminth-HIV, and helminth-TB infected-only data, we additionally evaluated the prevalence of helminth infections among those harboring a malaria, HIV, or TB infection using the Freeman-Tukey double arcsine transformation [27] to address the problems of confidence limits extending beyond the 0,1 range and variance instability [28]. We back-transformed the results to proportions using a formula derived for the inverse of the Freeman-Tukey double arcsine transformation [29]. Heterogeneity between studies was assessed using the \(I^2\) statistic [30]. We used fixed effects models where heterogeneity was not significant (\(I^2 < 50\%\)) and random-effects models for all other analyses. We used resampling methods to obtain bootstrapped 95% confidence intervals. We additionally conducted a meta-regression to evaluate the effect of a moderator variable, publication year, on the helminth-helminth polyparasitism mean difference outcome. All analysis was conducted using the ‘metafor’ package [31] in R statistical software version 3.4.1 [32].

To analyze Type II data, we compared the observed species density frequency distribution (number of individuals infected with 0, 1, 2, . . . N parasite species) from the collated field studies to the expected theoretical species density distribution computed using a null model developed by Janovy and colleagues to test for potential regularly occurring interspecies interactions [33]. This multiple-kind lottery model calculates the expected number of individuals infected with 0, 1, 2, . . . N parasite species assuming independence of parasitic infection events and using the prevalence of a parasite species as the probability of infection success. The expected theoretical distribution was computed in this study via the implementation of the step-wise recurrence algorithm developed by Janovy and colleagues (S1 Text) [33]. The observed species density frequency distributions obtained directly from the studies were compared to the model-calculated expected distributions using chi-squared tests. Deviations in the observed data from the model-computed expected distribution can result from several processes, such as competitive interactions among parasite species or high host heterogeneity to infection [26].

The main summary measure used for Type III association data was the odds ratio (OR) [95% Confidence Interval (CI)]. Adjusted odds ratios were used preferentially, and the crude and adjusted odds ratios were analyzed separately in addition to pooled. Studies with zero-count cells were adjusted by adding 0.5 to all cell counts [34]. Data was entered as log OR and variance of the log OR and a fixed effects or random effects model was run in the ‘metafor’ package [31] depending on the existence of significant between-study heterogeneity.

Study quality was assessed via a quality score computed using the NIH Quality Assessment Tool for Observational Cohort and Cross-sectional Studies and the NIH Quality Assessment Tool for Case-Control Studies [35]. Quality assessment for cohort and cross-sectional study designs was conducted differently for the Types I and II data and the Type III data due to their different objectives. For Types I and II data, which assessed prevalence and species density distributions, questions 6, 7, 13, and 14 were not included in the quality assessment score as they
were not applicable to cross-sectional prevalence studies. The quality assessment score for Type III association data, and Type I and III case-control studies included all questions. Quality assessment scores are reported as percentages obtained by dividing the number of studies reporting a “Yes” answer to each included question by the number of included questions.

Reporting bias was assessed using visual inspection of funnel plots and statistical evaluation using Egger’s regression test, where bias is evident when $p < 0.1$.[36]

The following variables were extracted for all data: study design, age range, study site (country), treatment status of community, diagnostic method(s), and the data relevant to each type.

**Morbidity assessments**

We undertook morbidity assessments by including any study that statistically evaluated the difference in a morbidity outcome between polyparasitized and singly parasitized individuals or polyparasitized and not polyparasitized individuals. Reported polyparasitism combinations were characterized as either having a positive, neutral or negative effect on the specified morbidity outcome. Positive and negative effects indicate the polyparasitized individuals experience a significantly better or worse health outcome, respectively, while neutral effects indicate the difference in morbidity outcomes was statistically insignificant. Chi-squared tests were conducted to determine if the total counts of observed positive, negative and neutral outcomes differed from those expected assuming the null hypothesis of equal proportions, which provides a vote-counting method based on deriving parameters for assessing outcomes against confidence intervals ($\alpha = 0.05$)[23,37].

**Results**

A total of 3862 studies were identified using the search strategy followed in this study (Methods). After removing duplicates and irrelevant studies (based on perusal of information given in study titles and abstracts), we conducted full-text article assessments for eligibility on 499 of these studies, of which 211 were subsequently included in the meta-analysis (Fig 1). An overview of study characteristics for each analysis performed is presented in Table 1, while tables of individual study characteristics can be found in the Supplementary Information (S1–S5 Tables).

For the 211 studies included in the meta-analysis, study quality was rated as either good (>70%), fair (50–70%), or poor (<50%) for each type of data for which a study met the inclusion criteria (S6 and S7 Tables). All studies for Type I and Type II data were rated as either good or fair and were thus included in the analysis. For Type III data, studies were rated in all three categories; those rated as poor were not included in the meta-analysis due to the significant risk of bias[35].

Studies meeting the inclusion criteria for the meta-analyses of the mean prevalence difference between multiple and single infections numbered 50 for helminth-helminth studies[38–85], 40 for helminth intestinal-protozoa studies[45,47,53,59,86–120], 15 for helminth-malaria studies[63,66,75,121–132], 13 for helminth-TB[133–145], and 23 for helminth-HIV[146–168]. All type I mean difference analyses were conducted used random effects models due to significant heterogeneity, ranging from a helminth-malaria $I^2$ of 61.3% to a helminth-helminth $I^2$ of 91.6% (Fig 2, S1–S4 Figs). The prevalence of polyparasitized helminth-helminth and helminth-protozoa individuals exceeded the prevalence of singly-infected helminth and protozoa individuals by 14.0% (95% CI 4.6–23.4%) and 14.7% (5.3–24.0%), respectively (Figs 2 and 3A, S1 Fig). For helminth-malaria, helminth-HIV, and helminth-TB, the prevalence of malaria-helminth, HIV-helminth and TB-helminth co-infected individuals was less than the prevalence of individuals singly-infected with malaria, HIV, and TB, respectively, with mean...
differences of -12.0% (-22.5 - -1.4%) for helminth-malaria, -29.5% (-45.1 - -13.8%) for helminth-HIV, and -32.1% (-53.1 - -11.1%) for helminth-TB (Fig 3A, S2–S4 Figs). However, it is important to note that among those infected with malaria, HIV, and TB, the prevalence of helminth infections was notable; among malaria-infected individuals, 41.7% (29.8–54.1%) were co-infected with at least one helminth infection (Fig 3B). Similarly, 31.5% (21.4–42.4%) of TB-positive individuals harbored at least one helminth infection and 29.7% (21.4–38.8%) of HIV-positive individuals were co-infected with at least one helminth infection (Fig 3B, S5–S7 Figs). The Egger’s Regression Test for Funnel Plot Asymmetry indicated bias for the mean difference Type I helminth-malaria studies (p = 0.085) and helminth-HIV studies (p = 0.007), but none for the helminth-only (p = 0.589), helminth-protozoa (p = 0.233), and helminth-TB (p = 0.520) studies. For the proportion of helminth co-infected individuals among those malaria-,
Table 1. Overview of study characteristics for studies included in the meta-analyses performed for the three different types of data: Type I (single and multiple infection prevalence data), Type II (prevalence of host infection status class, from C = 0 for uninfected hosts to C = N for maximally-infected hosts), and Type III (association data). PSAC = pre-school aged children; SAC = school-aged children.

| Data Type | Parasite Combination | Number of Studies | Study Population* | Continent | Single Infection* | Multiple Infection* | Refs |
|-----------|----------------------|-------------------|-------------------|-----------|------------------|---------------------|------|
| **Type I** | Helminth-Helminth   | 50                | PSAC: 5 SAC: 20   | Africa: 23 Asia: 20 North America: 3 South America: 4 | 2.8% - 58.0% | 0.1% - 95.2% | [38–85] |
|           |                      |                   | Adults: 1 Combination: 23 |           |                  |                     |      |
|           |                       | 40                | PSAC: 4 SAC: 13   | Africa: 11 Asia: 17 North America: 3 South America: 9 | 8.4% - 42.0% | 1.1% - 87.3% | [45,47,53,59,86–120] |
|           |                      |                   | Adults: 1 Combination: 21 |           |                  |                     |      |
|           | Helminth-Malaria     | 15                | PSAC: 1 SAC: 8   | Africa: 13 Asia: 1 North America: 0 South America: 1 | 5.9% - 61.0% | 3.4% - 64.1% | [63,66,75,121–132] |
|           |                      |                   | Adults: 0 Combination: 6 |           |                  |                     |      |
|           | Helminth-Tuberculosis| 13                | PSAC: 1 SAC: 0   | Africa: 8 Asia: 2 North America: 0 South America: 3 | NA       | 7.6% - 70.9% | [133–145] |
|           |                      |                   | Adults: 9 Combination: 3 |           |                  |                     |      |
|           | Helminth-HIV         | 23                | PSAC: 0 SAC: 0   | Africa: 18 Asia: 4 North America: 0 South America: 1 | NA       | 1.9% - 69.4% | [146–168] |
|           |                      |                   | Adults: 14 Combination: 9 |           |                  |                     |      |
| **Type II** | Helminth-Helminth   | 30                | PSAC: 4 SAC: 14  | Africa: 10 Asia: 15 North America: 2 South America: 3 | 2.8% - 58.0% | 0.1% - 95.2% | [38,39,41–44,47,48,51–56,58,63,64,68,70,72,73,76–79,81–84] |
|           |                      |                   | Adults: 0 Combination: 12 |           |                  |                     |      |
|           | Helminth-Protozoa    | 18                | PSAC: 4 SAC: 6   | Africa: 4 Asia: 9 North America: 2 South America: 3 | 8.4% - 40.3% | 1.5–78.3% | [47,53,86–92,95,97,101,102,110,112,113,116,119] |
|           |                      |                   | Adults: 0 Combination: 8 |           |                  |                     |      |

(Continued)
| Data type | Parasite Combination | Number of studies | Study Population | Continent | Single Infection | Multiple Infection | Refs |
|-----------|----------------------|-------------------|------------------|-----------|-----------------|-------------------|------|
| Type III  | Helminth-Helminth    | 113               | PSAC: 6          | Africa: 82, Asia: 23, North America: 0, South America: 8 | NA               | 1.28–4.21         | [41,45,48,49,51,52,60,63,64,66,75,80,81,85,95,99,104,106,110,111,115,124,131,169–191] |
|           |                      |                   | SAC: 49          |           |                 |                   |      |
|           |                      |                   | Adults: 7        |           |                 |                   |      |
|           |                      |                   | Combination: 51  |           |                 |                   |      |
|           | Helminth-Malaria     | 56                | PSAC: 6          | Africa: 53, Asia: 0, North America: 0, South America: 3 | NA               | 0.84–1.49         | [63,66,75,121,124,125,128,131,171,173,175,187,192–206] |
|           |                      |                   | SAC: 30          |           |                 |                   |      |
|           |                      |                   | Adults: 1        |           |                 |                   |      |
|           |                      |                   | Combination: 19  |           |                 |                   |      |
|           | Helminth-Tuberculosis| 16                | PSAC: 0          | Africa: 14, Asia: 0, North America: 0, South America: 2 | NA               | 1.31–1.88         | [133,134,136,138,141,142,145,207] |
|           |                      |                   | SAC: 0           |           |                 |                   |      |
|           |                      |                   | Adults: 9        |           |                 |                   |      |
|           |                      |                   | Combination: 6   |           |                 |                   |      |
|           | Helminth-HIV         | 45                | PSAC: 0          | Africa: 31, Asia: 4, North America: 0, South America: 10 | NA               | 0.88–2.13         | [155,156,158,161–163,166,207–215] |
|           |                      |                   | SAC: 0           |           |                 |                   |      |
|           |                      |                   | Adults: 13       |           |                 |                   |      |
|           |                      |                   | Combination: 31  |           |                 |                   |      |

*Refers to the range in prevalence for Type I and II prevalence studies and the range in computed odds ratios for Type III association studies

+Combination refers to any combination of the age groups PSAC, SAC and Adults

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HIV-, and TB-positive individuals, no bias was indicated for the helminth-malaria (p = 0.818), helminth-HIV (p = 0.361), or helminth-TB (p = 0.734) studies. Additionally, the meta-regression analysis indicated a downward trend in the helminth polyparasitism mean difference (helminth polyparasitism prevalence–helminth monoparasitism prevalence) over time (Fig 4), although this trend was only approaching significance (coefficient -0.008 [95% CI -0.017–0.001], p = 0.072).

A total of 30 helminth-only [38,39,41–44,47,48,51–56,58,63,64,68,70,72,73,76–79,81–84] and 18 helminth-intestinal protozoa [47,53,86–92,95,97,101,102,110,112,113,116,119] studies provided categorical data concerning the number of parasites in each host and were evaluated using the Janovy model. Twenty studies demonstrated significantly different observed frequency distributions of infection compared to the frequency of host infection expected in each host class if infections were independent events for helminth-only studies, while ten studies
demonstrated significant differences in these distributions for helminth-intestinal protozoa studies (Tables 2 and 3). For both helminth-only and helminth–protozoa infections, most studies found greater than expected numbers of individuals infected with zero and greater than two parasites, while the majority of studies found fewer than expected numbers of individuals infected with one and two parasites (Fig 5).

A total of eight helminth-helminth, five helminth-malaria, five helminth-HIV, and three helminth-TB parasite pairs had at least five studies with study quality ≥ 50% and were thus included in the Type III meta-analyses (Table 4). Both fixed and random-effects models were run for the above parasite pairs based on absence or presence of significant between-study heterogeneity given that $I^2$ values for the different parasite pairs varied from 0% to 90%. Seven of the eight helminth-only pairs demonstrated a significant positive association (Table 4, Fig 6 and S8–S14 Figs), with the *A. lumbricoides*-*T. trichiura* pairing overall showing the association of highest magnitude. Our findings indicate that *S. stercoralis* was the only parasite found to be
significantly positively associated with both HIV and TB (OR 2.13 [1.13–4.02] and 1.88 [1.36–2.61], respectively) (Figs 7 and 8), while hookworm and *S. mansoni* were the two parasites found to be significantly positively associated with malaria (OR 1.35 [1.08–1.69] and OR 1.49 [1.04–2.14], respectively) (Table 4 and S15–S19 Figs). Overall, no parasite pairs exhibited a statistically significant negative association. The following parasite pairs exhibited bias based on Egger’s test: hookworm-HIV (p = 0.054), *S. stercoralis*-TB (p = 0.015), *A. lumbricoides*-hookworm (p = 0.054), *T. trichiura*-hookworm (p = 0.078), and *T. trichiura*-S. *stercoralis* (p = 0.001).

From the studies included in our meta-analysis, we identified three broad groups of morbidity-related outcomes for which multiple studies existed (Table 5): anemia prevalence, hemoglobin levels, and growth-related outcomes (Fig 9). Nine studies reporting differences in anemia prevalence between individuals with multiple infections compared to individuals with either single infections or no multiple infections showed 10 negative, 6 neutral, and 0 positive effects respectively on human health (Table 5). Of the studies providing data on the difference in hemoglobin levels, the most common observation was that multiply-infected individuals had significantly lower hemoglobin levels; we classified 7 negative, 6 neutral, and 2 positive effects on human health from 11 studies. Seven studies provided information on growth-related outcomes; from these studies we classified 8 negative, 16 neutral, and 0 positive effects from a range of indicators including BMI, stunting, age-for-height, and weight-for-height. The pattern of observed effects was significantly different than that expected assuming the null model of equal proportions for anemia prevalence ($X^2 = 9.5$, df = 2, $p = 0.009$) and growth-related factors ($X^2 = 16.0$, df = 2, $p < 0.001$), while the hemoglobin levels pattern was not statistically significant ($X^2 = 2.8$, df = 2, $p = 0.247$).
Table 2. Observed (O) and expected (E) species density frequency distributions of helminths in human hosts.

| Study [reference] | O/ E | total (n) | n = 0 | n = 1 | n = 2 | n = 3 | n = 4 | n = 5 | n = 6 | n = 7 | $X^2$ Statistic | p-value |
|-------------------|------|----------|-------|-------|-------|-------|-------|-------|-------|-------|-----------------|---------|
| Wong et al., 2016 [84] | O | 33 | 1 | 8 | 15 | 9 | | | | | 0.063 | 0.996 |
| E | 1 | 8 | 16 | 9 | | | | | | | | |
| Gordon et al., 2015 [51] | O | 545 | 10 | 85 | 196 | 188 | 66 | | | | 4.434 | 0.3504 |
| E | 6 | 81 | 208 | 191 | 59 | | | | | | | |
| Hu et al., 2015 [54] | O | 1403 | 1363 | 39 | 1 | 0 | | | | | 0.598 | 0.8968 |
| E | 1362 | 41 | 0 | 0 | | | | | | | | |
| Ferreira et al., 2015 [47] | O | 444 | 121 | 131 | 168 | 21 | 3 | 0 | 0 | | 55.577 | <0.001* |
| E | | 81 | 204 | 142 | 17 | 1 | 0 | 0 | | | | |
| Vonghachack et al., 2014 [82] | O | 729 | 81 | 172 | 276 | 169 | 31 | 0 | 0 | | 48.268 | <0.001* |
| E | | 44 | 210 | 301 | 152 | 20 | 1 | 0 | 0 | | | | |
| Sanchez et al., 2013 [70] | O | 320 | 88 | 129 | 76 | 27 | | | | | 47.863 | <0.001* |
| E | | 62 | 164 | 83 | 10 | | | | | | | | |
| Odiere et al., 2012 [68] | O | 4064 | 1398 | 2356 | 296 | 13 | 1 | | | | 1.769 | 0.778 |
| E | | 1399 | 2342 | 312 | 11 | 0 | | | | | | | |
| Muller et al., 2011 [63] | O | 156 | 17 | 51 | 76 | 11 | 1 | | | | 10.949 | 0.027* |
| E | | 9 | 65 | 72 | 10 | 0 | | | | | | | |
| Anah et al., 2008 [39] | O | 350 | 176 | 133 | 39 | 2 | | | | | 10.783 | 0.013* |
| E | | 162 | 159 | 28 | 1 | | | | | | | | |
| Tengco et al., 2008 [77] | O | 1990 | 879 | 797 | 293 | 21 | | | | | 139.413 | <0.001* |
| E | | 762 | 1016 | 206 | 6 | | | | | | | | |
| Jardim-Botelho et al., 2008 [56] | O | 196 | 14 | 51 | 94 | 37 | | | | | 2.057 | 0.561 |
| E | | 10 | 56 | 93 | 37 | | | | | | | | |
| Fleming et al., 2006 [48] | O | 1332 | 231 | 294 | 554 | 253 | 0 | 0 | 0 | | 186.136 | <0.001* |
| E | | 116 | 458 | 547 | 209 | 5 | 0 | 0 | 0 | | | | |
| Briand et al., 2005 [43] | O | 474 | 327 | 140 | 7 | 0 | 0 | | | | 0.574 | 0.966 |
| E | | 329 | 136 | 9 | 0 | 0 | | | | | | | |
| Tchuem Tchuente et al., 2003 [76] | O | 1044 | 102 | 287 | 358 | 286 | 11 | | | | 72.745 | <0.001* |
| E | | 60 | 293 | 458 | 229 | 5 | | | | | | | |
| Thiong'o et al., 2001 [78] | O | 3158 | 1017 | 1219 | 654 | 225 | 43 | | | | 130.172 | <0.001* |
| E | | 891 | 1356 | 732 | 166 | 13 | | | | | | | |
| Brooker et al., 2000 [44] | O | 1738 | 146 | 462 | 542 | 485 | 103 | | | | 132.655 | <0.001* |
| E | | 79 | 451 | 726 | 414 | 69 | | | | | | | |
| Lili et al., 2000 [58] | O | 766 | 190 | 302 | 197 | 77 | | | | | 41.157 | <0.001* |
| E | | 162 | 344 | 218 | 42 | | | | | | | | |
| Scolari et al., 2000 [72] | O | 236 | 113 | 69 | 53 | 1 | | | | | 37.366 | <0.001* |
| E | | 94 | 111 | 30 | 1 | | | | | | | | |

(Continued)
Although studies have suggested the ubiquity of polyparasitism in the tropics [20,21], a systematic assessment of the frequency, magnitude, direction and clinical outcome of co-infections between the major human helminths and other pathogens has been lacking. This is despite increasing recognition that host co-infection with multiple pathogens is the norm, and that a better quantitative understanding of the nature and extent of polyparasitism can have important epidemiological, clinical and control implications [3,5,14,22,23].

Here, we have conducted analyses of the available published data on the occurrence of helminth polyparasitism to provide a first comprehensive assessment of the extent, nature and health consequences of helminth co-infection in humans. Our results indicate overall that co-infection with helminths is generally more prominent and produces poorer host health outcomes compared with single infections, irrespective of the diversity of inter-parasite associations studied, although this outcome is less apparent in the case of some interspecies infections Table 2.

### Table 2. (Continued)

| Study [reference] | O/ E total (n) | n = 0 | n = 1 | n = 2 | n = 3 | n = 4 | n = 5 | n = 6 | X² Statistic | p-value |
|------------------|---------------|------|------|------|------|------|------|------|-------------|---------|
| Widjana et al, 2000 [83] | O 2394 | 312 | 689 | 995 | 381 | 17 | 218.714 | <0.001* |
| Toma et al., 1999 [79] | O 654 | 60 | 239 | 241 | 114 | 20.663 | 0.001* |
| Booth et al., 1998 [41] | O 1539 | 3 | 91 | 541 | 904 | 7.352 | 0.061 |
| Needham et al., 1998 [64] | O 543 | 8 | 43 | 233 | 259 | 18.919 | <0.001* |
| Albonico et al., 1997 [38] | O 3497 | 10 | 167 | 979 | 2350 | 68.350 | <0.001* |
| Booth et al., 1996 [42] | O 1276 | 45 | 563 | 569 | 99 | 0.975 | 0.807 |
| Upatham et al., 1989 [81] | O 1142 | 92 | 326 | 444 | 280 | 194.919 | <0.001* |
| Upatham et al., 1989 [81] | O 518 | 17 | 125 | 277 | 99 | 11.208 | 0.011* |
| Holland et al., 1987 [53] | O 140 | 77 | 30 | 20 | 12 | 1 | 74.177 | <0.001* |
| Higgins et al., 1984 [52] | O 1387 | 325 | 418 | 368 | 276 | 275.53 | <0.001* |
| Ismid et al., 1981 [55] | O 158 | 15 | 51 | 79 | 13 | 5.375 | 0.146 |
| Sinniah et al., 1978 [73] | O 150 | 27 | 54 | 56 | 13 | 2.372 | 0.499 |

* Indicates statistical significance (p<0.05)

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### Discussion

Although studies have suggested the ubiquity of polyparasitism in the tropics [20,21], a systematic assessment of the frequency, magnitude, direction and clinical outcome of co-infections between the major human helminths and other pathogens has been lacking. This is despite increasing recognition that host co-infection with multiple pathogens is the norm, and that a better quantitative understanding of the nature and extent of polyparasitism can have important epidemiological, clinical and control implications [3,5,14,22,23].

Here, we have conducted analyses of the available published data on the occurrence of helminth polyparasitism to provide a first comprehensive assessment of the extent, nature and health consequences of helminth co-infection in humans. Our results indicate overall that co-infection with helminths is generally more prominent and produces poorer host health outcomes compared with single infections, irrespective of the diversity of inter-parasite associations studied, although this outcome is less apparent in the case of some interspecies infections.
Thus, our meta-analyses of infection prevalence data demonstrated that helminth polyparasitism was significantly more abundant than single infections for both helminth-helminth (d = 14.0%; CI 4.6–23.4%) and helminth-intestinal protozoa (d = 14.7%; CI 5.3–24.0%) infections (Fig 3A). By contrast, while this predilection for a higher level of co-infection was not found for malaria, TB, and HIV infections, it is notable that helminthiasis was still common among those hosts infected with these pathogens (Fig 3B). Similarly, assessment of the frequency distribution of species richness among different host classes revealed that for both helminth-helminth and helminth-

| Study [reference] | O/E total (n) | 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 | X² Statistic | p-value |
|------------------|--------------|----------------------------------------|--------------|---------|
| Chin et al., 2016 [95] | O 186 41 75 51 18 1 0 | 12.111 | 0.033** |
| E 26 84 60 14 1 0 |
| Al-Mekhlafi et al., 2016 [89] | O 1218 680 422 103 12 1 0 0 0 | 1.560 | 0.980 |
| E 671 436 100 10 0 0 |
| Mekonnen et al., 2016 [110] | O 1021 489 405 114 13 0 0 0 0 0 | 20.534 | 0.025*** |
| E 456 465 92 7 0 0 0 0 0 0 0 0 |
| Bless et al., 2015 [91] | O 228 68 83 52 19 6 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 | 13.593 | 0.403 |
| E 56 97 57 16 2 0 0 0 0 0 0 0 0 0 0 |
| Ahmad et al., 2014 [86] | O 131 118 11 2 0 0 0 | 1.651 | 0.949 |
| E 117 14 1 0 0 |
| Ferreira et al., 2015 [47] | O 444 59 127 178 69 11 0 0 0 0 0 | 8.714 | 0.559 |
| E 46 151 167 71 9 0 0 0 0 0 0 |
| Munoz-Antoli et al., 2014 [112] | O 382 27 56 79 78 65 36 25 11 3 2 0 0 0 0 0 0 0 0 0 | 152.890 | <0.001*** |
| E 5 34 84 109 86 45 16 4 1 0 0 0 0 0 0 0 0 0 0 0 0 0 |
| Schar et al., 2014 [116] | O 218 27 64 72 36 15 3 1 0 0 0 0 0 0 0 0 0 0 | 4.154 | 0.994 |
| E 21 68 74 40 12 2 0 0 0 0 0 0 0 0 0 0 0 0 0 0 |
| Al-Delaimy et al., 2014 [88] | O 498 8 140 189 88 54 19 0 | 89.734 | <0.001*** |
| E 5 114 207 132 36 4 0 |
| Boonjaraspyino et al., 2013 [92] | O 253 159 79 15 0 0 0 0 0 0 0 0 | 2.186 | 0.998 |
| E 156 85 11 1 0 0 0 0 0 0 0 0 |
| Verhagen et al., 2013 [119] | O 390 126 122 89 46 7 0 0 | 29.274 | <0.001*** |
| E 97 159 100 30 4 0 0 |
| Goncalves et al., 2011 [102] | O 133 94 30 9 0 0 0 0 0 0 0 0 | 15.201 | 0.086 |
| E 71 48 12 1 0 0 0 0 0 0 0 0 |
| Nematian et al., 2008 [113] | O 19209 15675 3150 365 19 0 0 0 0 0 0 | 134.055 | <0.001*** |
| E 15519 3453 231 6 0 0 0 0 0 0 0 |
| Al-Agha et al., 2000 [87] | O 209 119 77 10 3 0 0 | 5.797 | 0.327 |
| E 120 74 15 1 0 0 |
| Gamboa et al., 1998 [101] | O 292 132 96 37 19 6 1 1 0 0 0 | 51.209 | <0.001*** |
| E 105 124 51 10 1 0 0 0 0 0 0 |
| Chunge et al., 1991 [97] | O 1129 212 250 234 230 134 52 13 4 0 0 0 | 240.781 | <0.001*** |
| E 99 299 362 239 98 27 5 1 0 0 0 0 |
| Holland et al., 1987 [53] | O 140 65 34 23 17 1 0 0 | 40.890 | <0.001*** |
| E 45 59 29 6 1 0 0 |
| Annan et al., 1986 [90] | O 422 126 130 97 47 21 1 0 0 0 0 0 0 | 30.134 | <0.001*** |
| E 83 172 121 39 6 1 0 0 0 0 0 0 0 |

* Indicates statistical significance (p<0.05)
intestinal protozoa studies, single and double infections are observed less than expected by chance, while uninfected host classes and host classes with greater than two species occurred more frequently than expected (Fig 5). Finally, our analysis of the direction and magnitude of the interspecies associations recorded (Table 4) show that while the majority of evaluated pairs of helminths were found to be significantly positively associated, signifying those infected with a specific helminth were significantly more likely to be infected with another compared to uninfected hosts, we found *S. mansoni* and hookworm to be the only two helminths significantly positively associated with malaria, whereas *S. stercoralis* was the only helminth exhibiting a significant positive association with TB and HIV.

A multitude of factors acting at various hierarchical levels from the within-host infra-parasite community level to the higher host community level could explain the observed positive associations between specific helminth and helminth, malaria, TB, and HIV pairs; such factors may include similar transmission routes, genetically-modified and immunologically-mediated host responses to infection, overlapping environmental distribution of parasite fauna, and commonly occurring social risk factors [216–219]. At the individual host level, an additional consideration is interspecies interactions, where specific helminth species can either interact within the human host with both other worms and microparasites directly in a negative or positive manner or act to regulate co-infections top-down via interactions with the host immune system [14,19]. If these bottom-up or top-down interspecies interactions among parasites in a host community are common and strong, then the distribution of within-host infracommmunity species richness would not be expected to simply reflect the prevalences of the various parasite species. Thus, the findings based on the Janovy null model analysis of the interspecies associations among helminth-helminth and helminth-protozoa communities, which showed in general that more studies reported a greater than expected numbers of individuals with zero infections or infected with greater than two parasites while the majority of studies found fewer than expected numbers of individuals infected with one or two parasites (Fig 5), could be due to shared common transmission routes [220,221], or modifications affected by either direct interactions between parasites or via the host immune system [17,18].
With regard to the involvement of helminth-mediated top-down control of microparasites through the immune system, several studies have suggested that helminth infection may alter host susceptibility to TB [5]; one study not only found an association between helminths and Table 4. Summary of computed odds ratios representing the association between helminth species, malaria, HIV, and TB.

| Parasite pair                  | Overall odds ratio | References                                      |
|-------------------------------|--------------------|------------------------------------------------|
| **Helminth-Helminth**         |                    |                                                 |
| A. lumbricoides + Hookworm    | 2.08 (1.68–2.57)*  | [41,45,48,51,52,60,63,64,66,68,81,95,110,124,131,171,172,176,179,189] |
| T. trichiura + Hookworm       | 2.58 (1.84–3.89)*  | [41,52,60,64,66,80,81,95,110,131,171,172,176,178,179,186,189] |
| A. lumbricoides + T. trichiura| 4.21 (3.21–5.52)*  | [41,45,48,60,64,66,75,80,81,85,95,99,110,111,115,131,170–172,174,179,184,188,189,191] |
| A. lumbricoides + S. mansoni  | 1.29 (0.87–1.91)   | [48,49,63,80,110,176,179,180,183,187]          |
| T. trichiura + S. mansoni     | 1.68 (1.10–2.55)*  | [45,80,110,176,179,180,183,187]               |
| Hookworm + S. mansoni         | 1.74 (1.28–2.37)*  | [48,63,80,104,106,110,131,175,184,185,187]   |
| T. trichiura + S. stercoralis | 2.43 (1.27–4.66)*  | [60,80,110,172,179,186]                       |
| S. haematobium + S. mansoni   | 2.19 (1.02–4.73)*  | [45,63,80,104,169,173,175,177,181,190]        |
| **Helminth-Malaria**          |                    |                                                 |
| Malaria + T. trichiura        | 0.87 (0.71–1.07)   | [66,75,128,131,194,195,199,202,206]            |
| Malaria + A. lumbricoides     | 0.84 (0.64–1.08)   | [63,66,75,124,131,192,194,195,199,202,206]    |
| Malaria + Hookworm:           | 1.35 (1.08–1.69)*  | [63,66,121,124,125,128,131,171,194,195,197,199,201,202,204–206] |
| Malaria + S. mansoni          | 1.49 (1.04–2.14)*  | [63,175,187,198,201,202]                      |
| Malaria + S. haematobium      | 1.34 (0.92–1.97)   | [63,121,128,131,173,193,196,200,202,203]      |
| **Helminth-HIV**              |                    |                                                 |
| HIV + T. trichiura:           | 1.09 (0.83–1.44)   | [156,158,161–163,166,208,210,213,215]         |
| HIV + A. lumbricoides:        | 1.05 (0.83–1.35)   | [156,161–163,166,208,210,213,215]             |
| HIV + Hookworm:              | 0.88 (0.57–1.36)   | [158,161–163,166,208,210,213,215]             |
| HIV + S. mansoni:            | 1.01 (0.85–1.21)   | [155,156,162,208–210,212,214]                 |
| HIV + S. stercoralis:         | 2.13 (1.13–4.02)*  | [158,161–163,207,208,210,211,215]             |
| **Helminth-TB**               |                    |                                                 |
| TB + S. stercoralis           | 1.88 (1.36–2.61)*  | [133,138,141,142,145,207]                     |
| TB + Hookworm:               | 1.65 (0.93–2.91)   | [133,136,138,141,142]                         |
| TB + A. lumbricoides:         | 1.31 (0.52–3.31)   | [133,134,138,141,142]                         |

* Indicates statistical significance (p<0.05)
TB but noted associations of increasing magnitude with an increasing number of helminths harbored [138]. Our study finding of positive associations between helminths and TB, with *S. stercoralis* being significant, supports this observation. By contrast, the effect of helminth co-infections on the clinical presentation of TB is not conclusive; some studies have found no significant effects of helminth infection on TB severity [134,137,222], while one study demonstrated that TB-helminth co-infected individuals have been found to have more advanced clinical presentation [144], although the extent to which this can be attributed to helminth-induced immunity changes or larval migration through the lungs remains unclear [5]. A study which found that deworming may result in a significant improvement in pro-inflammatory cytokine responses in latent-TB infected individuals which may reduce disease progression from latent to active TB suggests the importance of helminth-induced immunity changes in disease progression [223].

Researchers have hypothesized that helminth infections might increase one's susceptibility to HIV due to the helminth-induced strong T helper 2 (Th2) response and downregulation of the antiviral T helper 1 (Th1) response [224–226]; a recent study provided prospective data demonstrating lymphatic filariasis increased the likelihood of HIV infection [227]. Our findings of predominantly positive associations, although only one was significant, provide
support to this hypothesis. It is to be noted, here, that in addition to immunological factors, detrimental physical conditions, such as anemia and malnutrition, which are associated with helminthiasis, may also increase susceptibility to HIV and disease progression to AIDS [5]. A recent review on the effect of deworming medications on HIV disease progression concluded

Fig 7. Forest plots for the meta-analyses comparing the association between the helminth infections *A. lumbricoides*, hookworm, *T. trichiura*, *S. stercoralis*, *S. mansoni* and HIV infection. FE = fixed effects; RE = random effects.

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that while deworming of HIV-infected adults may positively affect HIV disease progression markers in a small and short-term manner, more research is needed to better understand this result [228].

Likewise for malaria, helminth-induced alteration of the balance between Th1 and Th2 type immune responses may increase susceptibility to malaria, although helminth-induced immunity is also thought to protect against severe complications of malaria [5,229]. However, population studies have provided conflicting reports of the relationship between helminths and malaria [229], although a recent review suggested these conflicting reports might be due to differences in the association of individual helminths with malaria [230], which is additionally reflected in this meta-analysis.

Ecological research into assembly rules structuring within-host parasite infracommunities suggests that apart from the action of factors at the host level, species richness in such parasite assemblages may also reflect the outcome of forces acting at the broader host community level [218]. Such factors may range from environmental and climatic variables that govern the biogeography of parasite and host species, including latitudinal gradient effects [218,231], epidemiological factors, such as exposure intensity, herd immunity and population density, to socio-economic factors that underlie host community sensitivity and adaptive response to parasitic infection [232–235]. This macroecological perspective to unravelling and predicting observed species richness in parasite assemblages means that investigative frameworks that can integrate species interactions at the within-host level with factors that govern parasite richness at the broader host community and ecological levels need to be developed and applied if
Table 5. Summary of morbidity outcomes reported by studies included in this meta-analysis which statistically evaluated the difference between poly-parasitized and singly parasitized or not parasitized individuals.

| Morbidity Outcome | Study [reference] | Parasite Combination | Comparison Specific Comparison | Statistical Analysis | Significance Meaning |
|-------------------|-------------------|----------------------|---------------------------------|----------------------|----------------------|
| Anemia            | Ezeamama et al., 2008 [46] | H-H MI vs not MI | MI (Moderate intensity) vs SI (low intensity) or NI | OR 2/3 S MI | |
|                   | Adedoja et al., 2015 [121] | H-H MI vs not MI | SH+HW+ vs not; SH+HN+ vs not; HW+HN+ vs not | OR 1/3 S 2/3 MI (1S); 1/3 MI | |
|                   | Sanchez et al., 2013 [70] | H-H MI vs SI vs NI | MI vs SI vs NI for AL, TT, and HW | X² | NS MI < SI but > NI |
|                   | Burdam et al., 2016 [123] | H-M MI vs SI | M+H+ vs SI | OR/AOR OR S/AOR NS | MI |
|                   | Sumbele et al., 2017 [75] | H-M-H/M MI vs SI | MI (PF+AL+ or PF+TT+ or AL+TT+) vs SI | X² | S MI |
|                   | Adedoja et al., 2015 [121] | H-M MI vs not MI | PF+SH+ vs not; PF+HW+ vs not; PF+HN+ vs not | OR 3/3 S MI | |
|                   | Humphries et al., 2011 [197] | H-M MI vs SI | HW+M+ vs not | OR NS MI | |
|                   | Njua-Yafi et al., 2016 [127] | H-M MI vs not MI | M+H+ vs not | OR NS MI | |
|                   | Arndt et al., 2013 [147] | H-HIV MI vs SI | HIV+/H+ vs HIV+/H- | PR S MI | |
|                   | Idindili et al., 2011 [153] | H-HIV MI vs SI | HIV + Helminths only vs HIV +H- | AOR S MI | |
| Hb levels         | Midzi et al., 2010 [126] | H-H MI vs SI | SCH vs. SCH +STH+ | MD S MI | |
|                   | Matangila et al., 2014 [61] | H-H MI vs SI vs NI | MI vs SI vs NI | ANOVA S MI lowest | |
|                   | Sanchez et al., 2013 [70] | H-H MI vs SI vs NI | MI vs SI vs NI | ANOVA NS MI < SI but > NI | |
|                   | Muller et al., 2016 [111] | H-H MI vs SI vs NI | AL+TT+ vs AL+TT- vs AL-+TT+ vs AL-+TT- | X² | S MI and 1 SI lowest |
|                   | Pullan et al., 2010 [204] | H-M MI vs not MI | HW+M+ vs not | Unclear S MI | |

(Continued)
Table 5. (Continued)

| Morbidity Outcome | Study [reference] | Parasite Combination | Comparison | Specific Comparison | Statistical Analysis | Significance | Meaning |
|-------------------|-------------------|----------------------|------------|---------------------|----------------------|--------------|---------|
|                    |                   |                      |            |                     |                      |              |         |
| Matangila et al., 2014 [61] | H-M | MI vs not MI | H+M+ vs not MI | t-test | S | MI ↓ |
| Sanchez-Arcila et al., 2014 [129] | H-M | MI vs SI | M+IPs+ vs IPs +M- | ANOVA | NS | MI ↓ |
| Sumbele et al., 2017 [75] | H-M | MI vs SI | (H-H or H-M) vs (H or M) | Mann Whitney U-test | S | MI ↓ |
| Midzi et al., 2010 [126] | H-M | MI vs SI | SCH vs. PF +SCH+STH+ | MD | S | MI ↓ |
| Kung’u et al., 2009 [199] | H-M | Interaction term of H*M predictor for Hb score | Regression | NS |
| Righetti et al., 2012 [205] | H-M | MI vs SI | PF+/HW+ vs PF+ | t-test | S: 8y/o; NS: 7y/o; MI ↓: 6y/o |
| Arndt et al., 2013 [147] | H-HIV | MI vs SI | HIV+vsH+/H- | PR | S | MI ↓ |
| Mhimbira et al., 2017 [142] | H-TB | MI vs SI | TB+/H+ vs TB +/H- | Unclear | S | MI ↑ |
| Stunting | Saldiva et al., 1999 [115] | H-H, H-P | MI vs not MI | TT+/AL+ vs not; TT+/GL + vs not; AL +/GL+ vs not | OR/AOR | S, 1 NS, 1 OR S/AOR | MI ↑ |
| Sanchez et al., 2013 [70] | H-H | MI vs SI vs NI | MI vs SI vs NI for AL, TT, and HW | X² | NS | MI highest |
| Muller et al., 2016 [111] | H-H | MI vs SI vs NI | AL+TT+ vs AL+TT- vs AL-TT+ vs AL-TT- | Unclear | S | MI highest |
| Height | Muller et al., 2016 [111] | H-H | MI vs SI vs NI | AL+TT+ vs AL+TT- vs AL-TT+ vs AL-TT- | Unclear | S | MI and I SI lowest |
| Nematian et al., 2008 [113] | H-P | MI vs SI | MI (3) vs MI [121] and MI [121] vs SI | t-test | NS | MI lowest |
| Height-for-age | Sanchez et al., 2013 [70] | H-H | MI vs SI vs NI | MI vs SI vs NI for AL, TT, and HW | ANOVA | NS | MI lowest |
| Quilhui-Cota et al., 2004 [114] | H-P | MI vs not MI | MI vs not MI for H and/or P | ANOVA | S | MI ↓ |
| Weight | Nematian et al., 2008 [113] | H-P | MI vs SI | MI (3) vs MI [121] and MI [121] vs SI | t-test | NS | MI lowest |
| Mhimbira et al., 2017 [142] | H-TB | MI vs SI | TB+/H+ vs TB +/H- | Unclear | NS | MI ↓ |

(Continued)
we are to better understand the forces that govern the observed helminth polyparasitic patterns uncovered in this study. This will also include the derivation and evaluation of process-driven hierarchical approaches if better mechanistic understandings of the transmission and control of the human helminths are to be ultimately achieved [18].

Of the studies included in this meta-analysis which evaluated morbidity outcomes, most exhibited negative effects of helminth co-infections on hemoglobin levels and anemia prevalence (Table 5; Fig 9). While the etiology of anemia is multifactorial [236], many of the diseases

Table 5. (Continued)

| Morbidity Outcome | Study [reference] | Parasite Combination | Comparison | Specific Comparison | Statistical Analysis | Significance | Meaning |
|-------------------|-------------------|----------------------|------------|---------------------|---------------------|-------------|---------|
| Weight-for-age    | Muller et al., 2016 [111] | H-H | MI vs SI vs NI | AL+TT+ vs AL+TT- vs AL-TT+ vs AL-TT- | Unclear | S | MI and SI lowest |
| Weight-for-height | Sanchez et al., 2013 [70] | H-H | MI vs SI vs NI | MI vs SI vs NI for AL, TT, and HW | ANOVA | S | MI ↓ |
| Weight-for-height | Quihui-Cota et al., 2004 [114] | H-P | MI vs not MI | MI vs not MI for H and/or P | Z score | S | MI ↓ |
| BMI               | Muller et al., 2016 [111] | H-H | MI vs SI vs NI | AL+TT+ vs AL+TT- vs AL-TT+ vs AL-TT- | Unclear | S | 1 SI lowest |
| BMI-for-age       | Mhimbira et al., 2017 [142] | H-TB | MI vs SI | TB+/H+ vs TB +/H- | Fisher’s Exact | NS | MI lowest |
| % thin            | Sanchez et al., 2013 [70] | H-H | MI vs SI vs NI | MI vs SI vs NI for AL, TT, and HW | ANOVA | NS | MI lowest |
| % underweight     | Sanchez et al., 2013 [70] | H-H | MI vs SI vs NI | MI vs SI vs NI for AL, TT, and HW | X² | NS | MI highest |
| % wasted          | Muller et al., 2016 [111] | H-H | MI vs SI vs NI | AL+TT+ vs AL+TT- vs AL-TT+ vs AL-TT- | Unclear | NS | MI and SI highest |
| Body fat %        | Mhimbira et al., 2017 [142] | H-TB | MI vs SI | TB+/H+ vs TB +/H- | S | MI ↓ |
| MUAC              | Mhimbira et al., 2017 [142] | H-TB | MI vs SI | TB+/H+ vs TB +/H- | NS | MI ↑ |
| Waist hip ratio   | Mhimbira et al., 2017 [142] | H-TB | MI vs SI | TB+/H+ vs TB +/H- | NS | MI = SI |

In the ‘meaning’ column, bold text denotes the morbidity outcome was worse among those multiply-infected, while italicized text denotes the morbidity outcome was better among those multiply-infected.

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studied in this meta-analysis are known to contribute to anemia, including malaria, schistosomiasis, hookworm, HIV and tuberculosis [237–240]. The proposed mechanisms by which these various diseases contribute to anemia vary, but an additive effect of such co-infections seems likely [22]. Thus, the finding that helminth co-infections are overwhelmingly associated with negative health outcomes of both higher anemia prevalences and lower hemoglobin levels is not unexpected. By contrast, the analyses evaluating growth-related variables were mostly neutral in outcome, although all statistically significant results were negative with no significant positive effects reported (Table 5). Malnutrition and associated poor growth outcomes have been found to be associated with helminth and intestinal protozoan infections [241,242], which comprise the bulk of the reviewed health effects, and thus the finding of either neutral or negative outcomes in this study is similarly not surprising. Nevertheless, the consistency of these detrimental effects observed across the range of pathogens investigated indicates that multiple infections associated with helminths generally result in worsened health outcomes. This result suggests that the health burden of helminthiases may be significantly underestimated currently. It also implies that more systematic holistic data on the outcomes of helminth polyparasitism, including co-infection with pathogens types that were not represented in the present studies, will be required if more accurate estimates of helminth disease burden is to be quantified.

A positive finding for disease control efforts from this study is that helminth-helminth polyparasitism prevalence appears to be decreasing over time (Fig 4), although this finding was only approaching significance (p = 0.072). This general trend can likely be attributed to deworming programs being instituted in endemic countries, although development may also be contributing to this decline. Overall, this result suggests the benefit of continuing deworming programs to reduce the prevalence of helminth polyparasitism. However, this analysis was limited by the dependence in this study on published data in the literature; while this meta-analysis was based on epidemiological studies conducted in endemic countries, these collated studies are not necessarily representative of the different geographies as they were not designed to obtain a representative sample of helminth prevalence within a political boundary. Routine surveillance data with a consistent approach to measuring and reporting polyparasitism would provide more accurate estimates and allow for additional analysis of trends in the data.

These study findings also have important implications for global health interventions seeking to alleviate the disease burden. There is a tendency in medicine and public health to

Fig 9. Direction of reported health outcomes of helminth co-infections for (a) hemoglobin levels, (b) anemia prevalence, and (c) growth-related variables. Horizontal line indicates expected value assuming the null hypothesis of equal proportions.

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consider infectious diseases in isolation [21]; however, the findings of this paper challenge this inclination. Not only is polyparasitism common in the tropics, potential interactions between helminths and other co-infections may also exacerbate both susceptibility to and disease progression of major infectious diseases including malaria, TB, and HIV. Co-infected individuals largely exhibit more severe morbidity outcomes than those either singly infected or not co-infected. While the exact mechanisms by which helminths interact with microparasites to affect host susceptibility and disease progression require further research, our findings of frequent co-infections and positive associations support the call for integrating deworming into routine treatment of malaria, HIV, and TB [243–245]. While there recently has been an effort to integrate treatments of the helminthic neglected tropical diseases [243–245], the call to integrate deworming into malaria, TB, and HIV treatment protocols has largely gone unanswered [246]. A recent mathematical modelling exercise suggested that a mass drug administration strategy reducing lymphatic filariasis transmission could potentially increase malaria prevalence, underscoring the importance of taking an integrated approach to disease control [15,16]. Overall, our study results suggest that new community ecology-based frameworks that can combine biomedical research into interspecies interactions at the individual host level with epidemiological, social, and ecological studies of factors that drive parasite species diversity at the host community level, will be ultimately needed if we are to shed better light on the direct and indirect processes that structure within-host parasite communities, parasite pathology, and on methods to accomplish the control of such communities [13,14,18].

This meta-analysis has several limitations. Firstly, Egger’s regression test indicated seven of the twenty-nine analyses presented here exhibited reporting bias. This bias could be attributed to publication bias, whereby the results are influenced by the publication or non-publication of studies, or to language bias as we only accepted studies published in English. For three of the analyses with potential reporting biases, (Type I helminth-HIV and Type III hookworm-HIV and T. trichiura-hookworm), larger studies indicated higher prevalence or odds ratio. However, for the other four analyses (Type I helminth-malaria, Type III S. stercoralis-TB, A. lumbricoides-hookworm, and T. trichiura-S. stercoralis) the prevalence of co-infections and the associations may be overestimated as larger studies indicated lower prevalence or odds ratios. The asymmetry noted in the funnel plots could also be due to true heterogeneity, whereby there are differences in underlying risk in the different sampled communities [36]. An additional limitation of this study is that the diagnostic method used to detect helminths was predominantly microscopic examination of stool samples using the Kato-Katz technique [247]; this method is known to underestimate the prevalence of single and multiple helminth infections, particularly when only a single stool sample is conducted and in areas of low intensity infections [248,249]. Therefore, this meta-analysis likely underestimated the true prevalence of helminth polyparasitism and co-infections. An additional limitation is that Type III studies were largely cross-sectional in nature which precludes temporal analysis to evaluate if a specific parasitic infection affects susceptibility to an additional parasitic infection. Finally, the analysis is further limited by the lack of a consistent approach to studying polyparasitism and analyzing polyparasitism data as evidenced by the multiple analyses we conducted and the ineligibility of many studies for all types of analysis. A consistent methodology to quantify and evaluate polyparasitism would provide improved estimates of its magnitude and allow for additional analyses of patterns that could inform more targeted interventions to combat polyparasitism.

Supporting information
S1 Checklist. PRISMA checklist.
(DOC)
S1 Text. More detailed methodology for meta-regression and Type II data analysis.
(DOCX)

S1 Table. Study characteristics of Type I and II helminth-helminth studies included in the meta-analysis.
(DOCX)

S2 Table. Study characteristics of Type I and II helminth-protozoa studies included in the meta-analysis.
(DOCX)

S3 Table. Study characteristics of Type I helminth-malaria studies included in the meta-analysis.
(DOCX)

S4 Table. Study characteristics of Type I helminth-tuberculosis (TB) studies included in the meta-analysis.
(DOCX)

S5 Table. Study characteristics of Type I helminth-HIV studies included in the meta-analysis.
(DOCX)

S6 Table. Quality assessment scores for each study considered in this meta-analysis using the NIH Quality Assessment Tool for Observational Cohort and Cross-sectional Studies.
(DOCX)

S7 Table. Quality assessment scores for each study considered in this meta-analysis using the NIH Quality Assessment Tool for Case-Control Studies.
(DOCX)

S1 Fig. Mean community prevalence difference between humans infected with multiple helminth-intestinal protozoa infections compared to humans infected with a single helminth or intestinal protozoa infection.
(TIF)

S2 Fig. Mean community prevalence difference between humans co-infected with helminth and malaria infections compared to humans infected with a single malaria infection.
(TIF)

S3 Fig. Mean community prevalence difference between humans co-infected with helminth and HIV infections compared to humans infected with a single HIV infection.
(TIF)

S4 Fig. Mean community prevalence difference between humans co-infected with helminth and TB infections compared to humans infected with a single TB infection.
(TIF)

S5 Fig. Forest plot for the meta-analysis evaluating the proportion of helminth co-infected individuals among malaria-positive individuals.
(TIF)

S6 Fig. Forest plot for the meta-analysis evaluating the proportion of helminth co-infected individuals among HIV-positive individuals.
(TIF)
S7 Fig. Forest plot for the meta-analysis evaluating the proportion of helminth-infected individuals among tuberculosis (TB)-positive individuals.

(TIF)

S8 Fig. Forest plot for the meta-analysis comparing the association between *A. lumbricoides* (AL) and *T. trichiura* (TT). a = AL+/TT+; b = AL+/TT-; c = AL-/TT+; d = AL-/TT-; RE = random effects. Odds ratio compares the odds of *A. lumbricoides* infection among *T. trichiura*-positive individuals (a/c) compared to the odds of *A lumbricoides* infection among *T. trichiura*-negative individuals (b/d).

(TIF)

S9 Fig. Forest plot for the meta-analysis comparing the association between *T. trichiura* (TT) and hookworm (HW). a = TT+/HW+; b = TT+/HW-; c = TT-/HW+; d = TT-/HW-; RE = random effects. Odds ratio compares the odds of *T. trichiura* infection among hookworm-positive individuals (a/c) compared to the odds of *T. trichiura* infection among hookworm-negative individuals (b/d).

(TIF)

S10 Fig. Forest plot for the meta-analysis comparing the association between *T. trichiura* (TT) and *S. stercoralis* (SS). a = TT+/SS+; b = TT+/SS-; c = TT-/SS+; d = TT-/SS-; RE = random effects. Odds ratio compares the odds of *T. trichiura* infection among *S. stercoralis*-positive individuals (a/c) compared to the odds of *T. trichiura* infection among *S. stercoralis*-negative individuals (b/d).

(TIF)

S11 Fig. Forest plot for the meta-analysis comparing the association between *A. lumbricoides* (AL) and *S. mansoni* (SM). a = AL+/SM+; b = AL+/SM-; c = AL-/SM+; d = AL-/SM-; RE = random effects. Odds ratio compares the odds of *A. lumbricoides* infection among *S. mansoni*-positive individuals (a/c) compared to the odds of *A lumbricoides* infection among *S. mansoni*-negative individuals (b/d).

(TIF)

S12 Fig. Forest plot for the meta-analysis comparing the association between *S. mansoni* (SM) and hookworm (HW). a = SM+/HW+; b = SM+/HW-; c = SM-/HW+; d = SM-/HW-; RE = random effects. Odds ratio compares the odds of *S. mansoni* infection among hookworm-positive individuals (a/c) compared to the odds of *S. mansoni* infection among hookworm-negative individuals (b/d).

(TIF)

S13 Fig. Forest plot for the meta-analysis comparing the association between *T. trichiura* (TT) and *S. mansoni* (SM). a = TT+/SM+; b = TT+/SM-; c = TT-/SM+; d = TT-/SM-; RE = random effects. Odds ratio compares the odds of *T. trichiura* infection among *S. mansoni*-positive individuals (a/c) compared to the odds of *T. trichiura* infection among *S. mansoni*-negative individuals (b/d).

(TIF)

S14 Fig. Forest plot for the meta-analysis comparing the association between *S. haematobium* (SH) and *S. mansoni* (SM). a = SH+/SM+; b = SH+/SM-; c = SH-/SM+; d = SH-/SM-; RE = random effects. Odds ratio compares the odds of *S. haematobium* infection among *S. mansoni*-positive individuals (a/c) compared to the odds of *S. haematobium* infection among *S. mansoni*-negative individuals (b/d).

(TIF)
S15 Fig. Forest plot for the meta-analysis comparing the association between *A. lumbricoides* (AL) and malaria (M). 
- a = AL+/M+;
- b = AL+/M-;
- c = AL-/M+;
- d = AL-/M-;

RE = random effects. Odds ratio compares the odds of *A. lumbricoides* infection among malaria-positive individuals (a/c) compared to the odds of *A. lumbricoides* infection among malaria-negative individuals (b/d).
(TIF)

S16 Fig. Forest plot for the meta-analysis comparing the association between hookworm (HW) and malaria (M). 
- a = HW+/M+;
- b = HW+/M-;
- c = HW-/M+;
- d = HW-/M-;

RE = random effects. Odds ratio compares the odds of hookworm infection among malaria-positive individuals (a/c) compared to the odds of hookworm infection among malaria-negative individuals (b/d).
(TIF)

S17 Fig. Forest plot for the meta-analysis comparing the association between *T. trichiura* (TT) and malaria (M). 
- a = TT+/M+;
- b = TT+/M-;
- c = TT-/M+;
- d = TT-/M-;

RE = random effects. Odds ratio compares the odds of *T. trichiura* infection among malaria-positive individuals (a/c) compared to the odds of *T. trichiura* infection among malaria-negative individuals (b/d).
(TIF)

S18 Fig. Forest plot for the meta-analysis comparing the association between *S. haematobium* (SH) and malaria (M). 
- a = SH+/M+;
- b = SH+/M-;
- c = SH-/M+;
- d = SH-/M-;

RE = random effects. Odds ratio compares the odds of *S. haematobium* infection among malaria-positive individuals (a/c) compared to the odds of *S. haematobium* infection among malaria-negative individuals (b/d).
(TIF)

S19 Fig. Forest plot for the meta-analysis comparing the association between *S. mansoni* (SM) and malaria (M). 
- a = SM+/M+;
- b = SM+/M-;
- c = SM-/M+;
- d = SM-/M-;

RE = random effects. Odds ratio compares the odds of *S. mansoni* infection among malaria-positive individuals (a/c) compared to the odds of *S. mansoni* infection among malaria-negative individuals (b/d).
(TIF)

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