# Feasibility of interrupting the transmission of soil-transmitted helminths: the DeWorm3 community cluster-randomised controlled trial in Benin, India, and Malawi

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## Summary

**Background** Soil-transmitted helminths are targeted for elimination as a public health problem. This study assessed whether, with high coverage, community-wide mass drug administration (MDA) could lead to transmission interruption.

**Methods** DeWorm3 is an open-label, community cluster-randomised controlled trial in Benin, India, and Malawi. In each country, a single governmental administrative unit (population ≥80 000 individuals) with soil-transmitted helminth endemicity and participation in at least five rounds of community-wide MDA for lymphatic filariasis, was divided into 40 clusters (population ≥1650 individuals), which were randomly assigned (1:1) to community-wide MDA versus school-based deworming. Laboratory personnel were masked to exposure status and all investigators were masked to post-baseline outcome data until unmasking. In all clusters, preschool-aged and school-aged children received school-based deworming as per national guidelines for 3 years. In intervention clusters, door-to-door community-wide MDA (a single oral dose of 400 mg albendazole) was delivered to all eligible individuals biannually by community drug distributors for 3 years. All individuals aged 12 months and older in India and Benin and aged 24 months and older in Malawi were eligible for treatment, except women in the first trimester of pregnancy, those with adverse reactions to benzimidazoles, those who were acutely ill or intoxicated, or those reporting treatment within the previous 2 weeks. The co-primary outcomes were individual-level prevalence and cluster-level transmission interruption (ie, weighted prevalence of predominant species of ≤2%) of the predominant soil-transmitted helminth species, assessed by quantitative PCR (qPCR) 24 months after the last round of MDA. The analysis set contained a subset of randomly selected participants per cluster who enrolled in the endline assessment, provided a stool sample, and had a qPCR result. All individuals who received treatment were eligible for inclusion in the safety population. This trial is registered with ClinicalTrials.gov (NCT03014167), and is active but not recruiting.

**Findings** Between Oct 10, 2017, and Feb 17, 2023, 120 clusters (40 clusters per country, comprising 357 716 individuals) were randomly assigned, 60 to community-wide MDA and 60 to school-based deworming. 184 030 (51·4%) individuals in the clusters at baseline were female, 173 663 (48·5%) were male, and 23 (<0·1%) were other. The analysis set consisted of 58 827 individuals in the control group and 58 554 in the intervention group 24 months after the cessation of all deworming, *Necator americanus* prevalence (the predominant species at all sites) in the community-wide MDA group was lower than the school-based deworming group in Benin (adjusted prevalence ratio [aPR] 0·44 [95% CI 0·34–0·58]), India (0·41 [0·32–0·52]), and Malawi (0·40 [0·34–0·46]). Transmission interruption was achieved for *N americanus* in 11 (55%) of 20 intervention clusters versus six (30%) of 20 control clusters in Benin (p=0·20), in one (5%) intervention cluster versus no control clusters in India (p=1·00), and in no clusters in either group in Malawi (p=1·00). 984 adverse events were reported among 487 participants over the study, of which 32 among 13 participants resulted in hospitalisation and were classified as serious adverse events (three of which were related to study procedures).

**Interpretation** Soil-transmitted helminth transmission interruption might be possible in focal geographies but does not appear to be programmatically feasible within the evaluated timeframe. Community-wide MDA should be considered as an alternative strategy to school-based deworming programmes to improve equity and outcomes in helminth-endemic areas.

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See Online for appendix 1

## Research in context

### Evidence before this study

The current WHO target for soil-transmitted helminths is elimination as a public health problem, delivered through annual and biannual school-based deworming of at-risk groups, including preschool-aged and school-aged children. Previously developed mathematical models indicate that interruption of soil-transmitted helminth transmission might be feasible with intensified deworming. A 2024 systematic review and meta-analysis by Ugwu and colleagues provides further evidence that community-wide deworming interventions lead to greater reductions in soil-transmitted helminth prevalence than school-based deworming. It included studies that overlapped with the timeframe of the DeWorm3 study, but were limited by smaller sample sizes, shorter duration, and restricted geographical representativeness.

### Added value of this study

DeWorm3 was done in three different countries in Africa and Asia to ensure geographical representativeness. The overall population included in the study was large and the sample size of individuals who received the intervention and were evaluated for study outcomes allowed for robust estimation of the study objectives. In addition, the rigorous design of the study—as a cluster-randomised trial—allowed for assessment of the contribution of each intervention while limiting potential bias. Although transmission interruption was not achieved across all clusters, community-wide MDA led to substantially greater reductions in the prevalence of the predominant species of soil-transmitted helminth at all sites compared with school-based deworming.To our knowledge, this is the first large randomised controlled trial to assess the feasibility of interrupting the transmission of soil-transmitted helminths and is by far the largest trial to evaluate the impact of community-wide MDA.

### Implications of all the available evidence

Due to the reductions in soil-transmitted helminth prevalence shown (driven by the predominant species *Necator americanus*) both in our trial and in others, community-wide MDA should be considered as a strategy to achieve the stated WHO goal of elimination as a public health problem, particularly in areas with high baseline prevalence (as lower prevalence reduced morbidity at the population level). However, transmission interruption using community-wide MDA was not achieved at programmatically relevant scale within the 3-year timeframe of the study, which was the first trial to look at this endpoint. The data from this large, rigorous, and geographically representative study adds to the previous evidence, to directly inform policy and programmes in soil-transmitted helminth-endemic areas. The study adds evidence to support policy development as countries transition donor financing and assess the role of community-wide MDA in achieving global targets for addressing neglected tropical diseases. Our data can also be used to reparametrise existing models to better inform prevalence thresholds and treatment duration and frequency to inform future efforts to interrupt soil-transmitted helminths transmission. In addition, our trial showed the feasibility of using high-throughput molecular assays as an alternative to existing coproscopic methods to provide robust estimates of soil-transmitted helminth prevalence and intensity. Given the improved diagnostic performance of quantitative PCR over traditional microscopy, quantitative PCR should be used in research and programmatic settings in which prevalence and intensity are low to improve estimates.

## Introduction

WHO recognises 21 conditions as neglected tropical diseases (NTDs) that disproportionately affect populations living in poverty, half of which are targeted for either elimination or eradication under the existing WHO roadmap for NTDs.[1,2] Among these diseases, soil-transmitted helminths, including roundworm (*Ascaris lumbricoides*), whipworm (*Trichuris trichiura*), and hookworms (*Necator americanus* and *Ancylostoma duodenale*) are not currently targeted for elimination. Instead, the roadmap targets reduced morbidity (elimination as a public health problem, defined as <2% prevalence of moderate and heavy intensity infections) in 96% of endemic countries by 2030.[3]

Soil-transmitted helminths are among the most prevalent human infections, with an estimated 1·15 billion individuals in 87 low-income and middle-income countries considered at risk in 2022.[4] These infections are associated with substantial disease burden, accounting for 1·9 million disability-adjusted life-years annually, largely as a result of anaemia, malnutrition, and micronutrient deficiencies.[5] Soil-transmitted helminths have been associated with reduced school attendance, poor school performance, lower income earning potential, and reduced societal economic development.[6] WHO currently recommends targeting improved access to safe water, sanitation, and hygiene (WASH) facilities, behaviour change, and preventive chemotherapy with anthelmintic agents (largely benzimidazoles) in populations at highest risk of morbidity (preschool-aged [2–4 years] and school-aged [5–15 years] children, women of reproductive age, and groups at high occupational risk [eg, miners and agricultural workers]).[3,7] Our study defined preschool-aged children as ages 1–4 years.

Current national soil-transmitted helminth programmes are supported by a robust drug donation programme, through which more than 337 million doses were provided in 2023 alone.[8] Although reported coverage of preschool-aged and school-aged children often approaches or exceeds national targets, coverage for other populations at risk, including women of reproductive age, is considerably lower and often

ineffectively monitored. In addition, there is strong evidence that children are rapidly re-infected after treatment due to exposure to untreated individuals in the community and ongoing environmental contamination (of soil, water, or food with soil-transmitted helminth larvae or eggs).[9] Given the dioecious nature of these parasites and the inability for most soil-transmitted helminth species to complete their lifecycle within the human host, there is an unstable equilibrium of infection intensity and prevalence, below which transmission cannot be sustained. As a result, as infection numbers in a human population fall, the likelihood that transmission can be sustained within the population decreases.[10] Several modelling studies have suggested that biannual (every 6 months) community-wide mass drug administration (MDA), in which all eligible community members are treated, could achieve interruption of transmission of soil-transmitted helminths within 3 years, assuming high coverage of the entire population over each campaign round.[11,12] These models suggest that more than 90% of clusters in which the true prevalence is reduced to less than 2% do not bounce back to the pre-MDA endemic state, suggesting that transmission will be eliminated in most of these settings.[13] In addition, a number of previous studies have shown greater reductions in prevalence using community-wide MDA compared with school-based targeted deworming.[14] High-quality trial data demonstrating the feasibility of soil-transmitted helminth elimination are needed to support any potential change in guidelines or policy.

We tested the feasibility of interrupting soil-transmitted helminth transmission at study sites in Benin, India, and Malawi in a large community-wide, cluster-randomised trial. We identified areas where multiple previous rounds of community-wide MDA using albendazole had already been delivered by previous lymphatic filariasis programmes. We hypothesised that prevalence might already be reduced in these areas and six additional rounds at high coverage and targeting all eligible individuals would be sufficient to reduce infection prevalence below the threshold necessary to sustain transmission. We aimed to compare the prevalence of the predominant soil-transmitted helminth species and to establish whether transmission of the predominant species could be interrupted using community-wide MDA versus school-based deworming.

## Methods

### Study design and participants

DeWorm3 was a community-wide, cluster-randomised controlled trial comparing biannual community-wide MDA to standard-of-care school-based deworming conducted in Benin, India, and Malawi between Oct 10, 2017, and Feb 17, 2023. DeWorm3 was reviewed and approved by the National Ethics Committee for Health Research (002–2017/CNERS-MS) of the Ministry of Health in Benin, the London School of Hygiene & Tropical Medicine (12013), the College of Medicine Research Ethics Committee (P.04/17/2161) in Malawi, and the Christian Medical College Institutional Review Board in Vellore, India (10392). It was also approved by the Human Subjects Division at the University of Washington, WA, USA (STUDY00000180). The trial was registered at ClinicalTrials.gov (NCT03014167). Community advisory boards were established at each study site to guide and inform the appropriate implementation of study procedures and facilitate effective community engagement. A summary of the study methods are provided here and a detailed description of the methods has been published previously (appendix 2).[15] In each country, predefined geographical areas contained within a single governmental administrative unit and comprising at least 80 000 individuals were selected to be the study sites. Criteria for selection were baseline soil-transmitted helminth endemicity, participation in at least five rounds of community-wide MDA for lymphatic filariasis, no active lymphatic filariasis programmes in the area, and existing support from national soil-transmitted helminth programmes. A census of the entire population was conducted at baseline (before randomisation and MDA delivery) and updated in years 2, 3, and 5. During each census, each site was visualised using mapping software available online (Bing, Google Satellite, and OpenStreetMap XYZ raster tiles in qGIS). All potential structures were identified from these maps and cross-referenced with visited structures to ensure the entire population of each study site was enumerated, including individuals considered migratory. The head of household or other adult household member consented to participation in the baseline census and annual updates on behalf of their households. Data collected during the census included demographic information (the head of the household or responding adult provided the sex of all household members, the options for which were male, female, and other), occupation, assets, household construction materials, and access to WASH. Data on ethnicity were collected and reported per standard country reporting guidance. WASH facilities were grouped and categorised according to the 2017 WHO–UNICEF Joint Monitoring Programme criteria.[16] Following the baseline census, each study site was divided into 40 clusters, each with a minimum population of 1650 individuals and adhering to local administrative boundaries where possible.

At baseline, 150 participants per cluster were sampled by age-stratified random sampling to include 30 preschool-aged children, 30 school-aged children, and 90 adults, who were tested for infection by the Kato–Katz technique and enrolled in a cohort to be followed annually. A further 500 individuals were selected by true random sampling from the list of cluster residents with a target of enrolling and collecting stool samples from 20 000 participants per site. To assess baseline

See Online for appendix 2

For **OpenStreetMap** see https://www.openstreetmap.org

prevalence, all participants enrolled in the cohort and were tested by quantitative PCR (qPCR). Due to resource constraints, a further 250 of the 500 cross-sectionally sampled individuals per cluster were selected and tested by qPCR. Participants who provided stool samples provided either written or witnessed oral consent, and children older than 7 years provided assent. Individuals who consented but did not provide a stool sample were excluded from prevalence analyses. All selected individuals who were found to have moderate or heavy-intensity soil-transmitted helminth infection by the Kato–Katz technique were treated with albendazole 400 mg.

### Randomisation and masking

Clusters were randomly assigned in a 1:1 ratio to community-wide MDA or school-based deworming. Laboratory personnel were masked to treatment allocation during assessment. Study investigators were masked to all prevalence and laboratory testing data post-baseline. The unmasked statistical team managed masked study data and conducted the final analysis as per the published statistical analysis plan (appendix 3) until the data lock occurred and unmasking to the study investigators occurred on Jan 18, 2024. The success of masking was not assessed. A lead member of the central DeWorm3 data team (KHÁ) used covariate-based restricted randomisation to ensure the clusters were balanced with regard to baseline soil-transmitted helminth prevalence as measured by the Kato–Katz technique, population size, age distribution, relative socioeconomic status, WASH access, and urban or rural designation of clusters. In addition randomisation in India was restricted to ensure balance of clusters in the Jawadhu Hills and Timiri subsites. Randomisation in Malawi was restricted to ensure the balance of clusters identified as potentially resistant to study activities by the site team. (appendix 1 p 2).[17] A simulation of 100 000 scenarios randomising 40 clusters 1:1 to two groups was done in Stata (version 14.2). For each main study site (one in each country), a scenario was then randomly selected from a list of scenarios that met balancing criteria (127 scenarios in Benin, 485 in India, and 297 in Malawi).

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### Procedures

In intervention clusters, a single oral dose of 400 mg of albendazole was provided biannually for 3 years via community-wide MDA by community drug distributors and volunteer members of the community selected to distribute drugs for diseases targeted by neglected tropical disease programmes. Community drug distributors were accompanied by study data collectors. Community-wide MDA treatment lists were based on the most recent census at that time and targeted all individuals eligible for treatment as per national guidelines (ages 12 months and older in India and Benin and 24 months and older in Malawi), with the exception of women who reported being in the first trimester of pregnancy, those with a history of adverse reactions to benzimidazoles, individuals who were acutely ill or intoxicated at the time of treatment, or those reporting treatment within the previous 2 weeks. Albendazole was provided to all eligible household members present at the visit and ingestion of the drug was directly observed when possible. Study staff made up to three attempts to visit each household and treatment was left at the household at the third visit for any individuals not reached over 1–2 weeks. Mop-up campaigns targeting untreated individuals were conducted in all intervention clusters within 1–2 weeks of each MDA round.

In all study clusters, eligible preschool-aged and school-aged children were treated in schools following country guidelines (ages 1–14 years in Benin, 1–19 years in India, and 2–19 years in Malawi) either annually (Benin and Malawi, coinciding with community-wide MDA rounds two, four, and six) or biannually (India, coinciding with all rounds of community-wide MDA). Non-enrolled preschool-aged and school-aged children were encouraged to go to schools for treatment in both India and Benin, but not in Malawi, as per existing national guidelines. Teachers, community drug distributors, or both recorded all treatments and documented whether treatment was directly observed. Once treated, the children had their finger marked with ink. In intervention clusters, school-based deworming preceded community-wide MDA and finger markings were used to ensure that children were not re-treated during campaigns that were conducted shortly after school-based deworming. As per agreements with local and national agencies, following the sixth round of community-wide MDA, no deworming was delivered in either study group for 24 months until the endline prevalence assessment was completed.

Cross-sectional assessments of soil-transmitted helminth prevalence were conducted at the end of the study (24 months following the sixth MDA round; 24 months after the sixth round of school-based deworming in India and approximately 30 months after the third round in Benin and Malawi). For each cluster, 1000 participants were randomly selected by true random sampling without stratification from the most recent census at that time with a target of enrolling and collecting stool samples from 40 000 participants per site (1000 per study cluster). Up to three attempts were made to reach each sampled individual, after which a replacement was selected from a backup sampling list. Individuals who consented but did not provide a stool sample were excluded from the study and were not part of the analysis set.

Prevalence (at both baseline and endline) was assessed using a multiplex qPCR assay that was

optimised and then validated in three laboratory sites.[15] Due to the very high sensitivity of the assay, cycle threshold cutoffs were set for *N americanus* and *A lumbricoides* to differentiate transmissible infections from detection of DNA more likely associated with non-transmissible ova or helminth fragments.[18] A finite mixture model was applied to the observed bimodal distributions of cycle threshold values observed at baseline, with a true positive qPCR result defined as any value with a 5% or greater chance of belonging to the primary peak. Values with a greater than 95% chance of belonging to the secondary peak were defined as indeterminate and samples with no amplification up to a cycle threshold of 40 (the number of cycles run) were considered negative. Given the very low sample numbers for *T trichiura* and *A duodenale*, all samples with a cycle threshold below 40 for these species were considered positive (appendix 1 p 3). All data were recorded electronically using Android phones with SurveyCTO software (Dobility; Cambridge, MA, USA).[19]

## Outcomes

There were two prespecified primary outcomes, individual-level soil-transmitted helminth infection and cluster-level transmission interruption, both measured by qPCR 24 months after the final round of treatment at each study site. Individual-level soil-transmitted helminth infection was defined as an individual's test result for the predominant baseline soil-transmitted helminth species (*A lumbricoides, A duodenale, N americanus,* or *T trichiura*). Cluster-level transmission interruption was defined as age-weighted and sex-weighted prevalence with finite population correction of the predominant baseline soil-transmitted helminth species with a one-sided 95% CI less than or equal to 2%, based on previously published studies.[12,13] The predominant soil-transmitted helminth species was established using the results of the baseline prevalence survey.

Prespecified secondary outcomes were to compare individual-level soil-transmitted helminth infection with any of the four predominant species and cluster-level transmission interruption for all four predominant species, defined as any prevalence less than or equal to 2% with 95% CIs following the methods as above. In intervention clusters, the prespecified outcome of treatment coverage was defined as the proportion of censused and eligible individuals who received albendazole at each round of community-wide MDA; individuals were reached by home visits, confirmed to be eligible, provided with treatment, directly observed taking treatment (doses were left for absent members), and were assessed using electronic MDA treatment registers, which were completed by study data collectors during house-to-house delivery of treatment.[19] In the control clusters, aggregate coverage of children in schools was assessed using routine treatment records collated by teachers, community drug distributors, or both, according to national programme requirements.[20]

Teachers and health workers were instructed to observe all treated individuals for adverse events following treatment. Adverse events were recorded by the study teams during and following MDA in the intervention group in India and Benin and in both groups in Malawi. In addition, all participants in both study groups were encouraged to report any adverse events that occurred after receipt of MDA to their local health facility or equivalent, where authorities were given contact information for reporting to the trial investigators. Adverse events were only classified as adverse events or serious adverse events, defined as hospitalisation, death, or both.

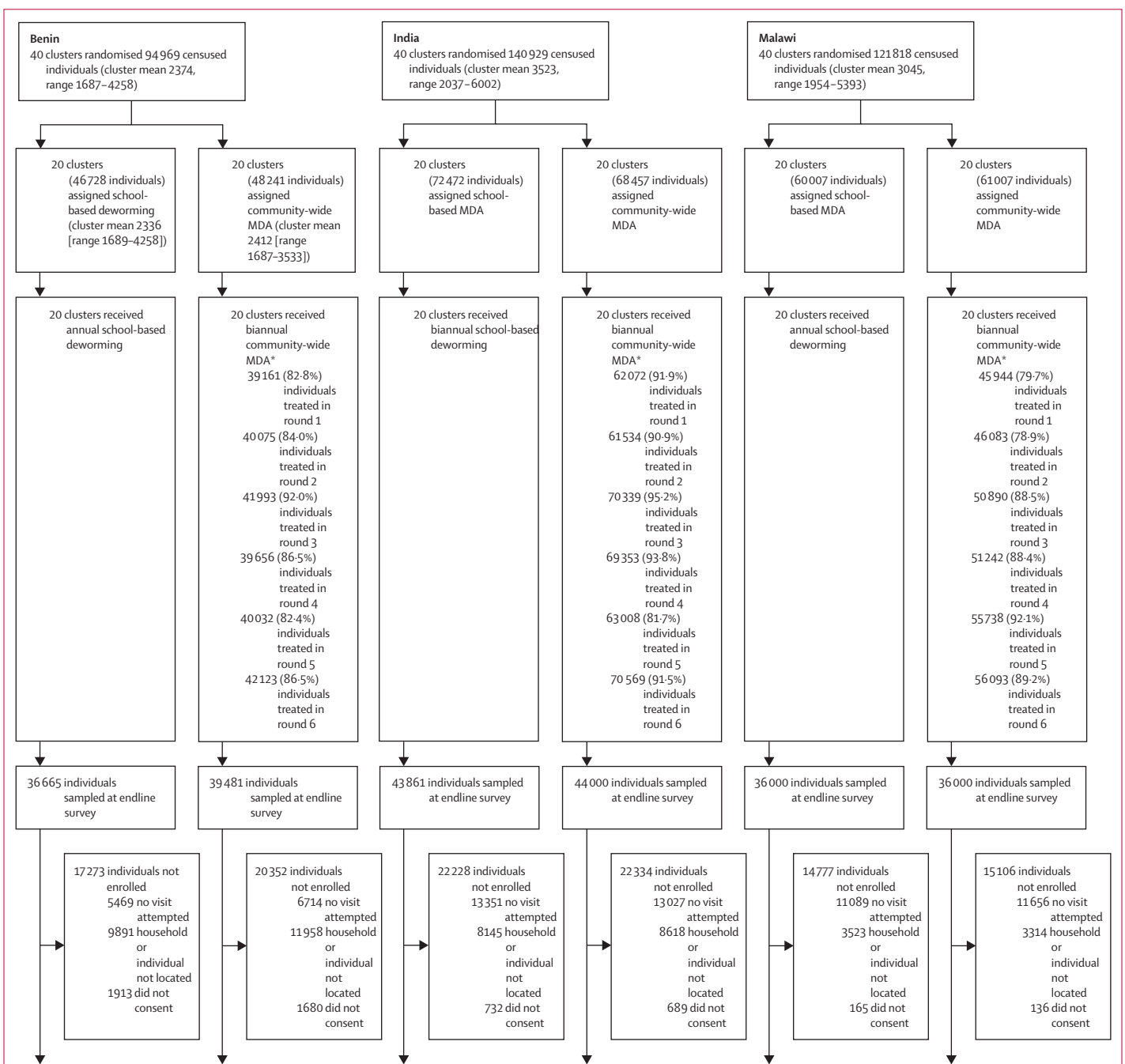
## Statistical analysis

All analyses and power calculations to detect differences in prevalence by group and in transmission interruption at the cluster level were conducted in R (version 4.4.2). A data safety and monitoring committee provided oversight. All details of the study protocol and statistical analysis plan were made publicly available before unmasking of data for analysis.[15] Simulations estimated power to detect a difference in the proportion of clusters in which transmission was interrupted by each group for each study site. Simulations assumed 20 clusters per group, 500 or 1000 individuals per cluster, a binomial distribution of soil-transmitted helminth prevalence with a mean prevalence of 7% across clusters in the control group and ranging from 0·1% to 4% ($\pi_1$) in the intervention group, an intraclass correlation coefficient (ICC) range of 0·003–0·05, and an $\alpha$ value of 0·05; 10 000 repetitions were run for each scenario (appendix 1 p 4). Measuring prevalence of soil-transmitted helminth infection among 1000 people per cluster at endline would provide adequate power for the transmission interruption objective in most scenarios given $\pi_1 \leq 2\%$. For the objective comparing endline prevalence by group, power was greater than or equal to 80% to detect a difference in endline prevalence up to a prevalence of 4% in the intervention group, given an ICC of ≤0·02 (appendix 1 p 5).

All analyses were conducted separately for each site unless otherwise specified. The effect of biannual community-wide MDA on prevalence of soil-transmitted helminths was analysed according to the group that the individual's cluster was assigned to, with a two-sided type I error rate of 0·05. Participants were included in the analysis set if, 24 months after the last round of community-wide MDA, they enrolled in the endline assessment and provided a stool sample that was correctly processed by the laboratory and obtained a qPCR result. For ease of interpretation, we estimated the effect as the prevalence ratio for each group using modified Poisson regression with robust variance estimation and exchangeable correlation matrix using generalised estimating equations, which adjusts SEs of the Poisson

model coefficients for binomial outcome[21] and accounts for the clustered study design.[22] Models were adjusted for age, sex, migration status, household size, population density within 0·5 km of the household, socioeconomic status (asset index quintile), WASH access, and cluster-specific age-weighted and sex-weighted baseline prevalence of soil-transmitted helminths. The effect of the intervention on the secondary outcome of prevalence of any soil-transmitted helminth was analysed in the same manner. Secondary analyses pooled data across all sites and tested for effect modification using an interaction term between study site and randomisation group.

The effect of biannual community-wide MDA on transmission interruption was tested using a Fisher's exact test comparing the proportion of clusters in each group achieving transmission interruption. The effect on the secondary outcome of transmission interruption of

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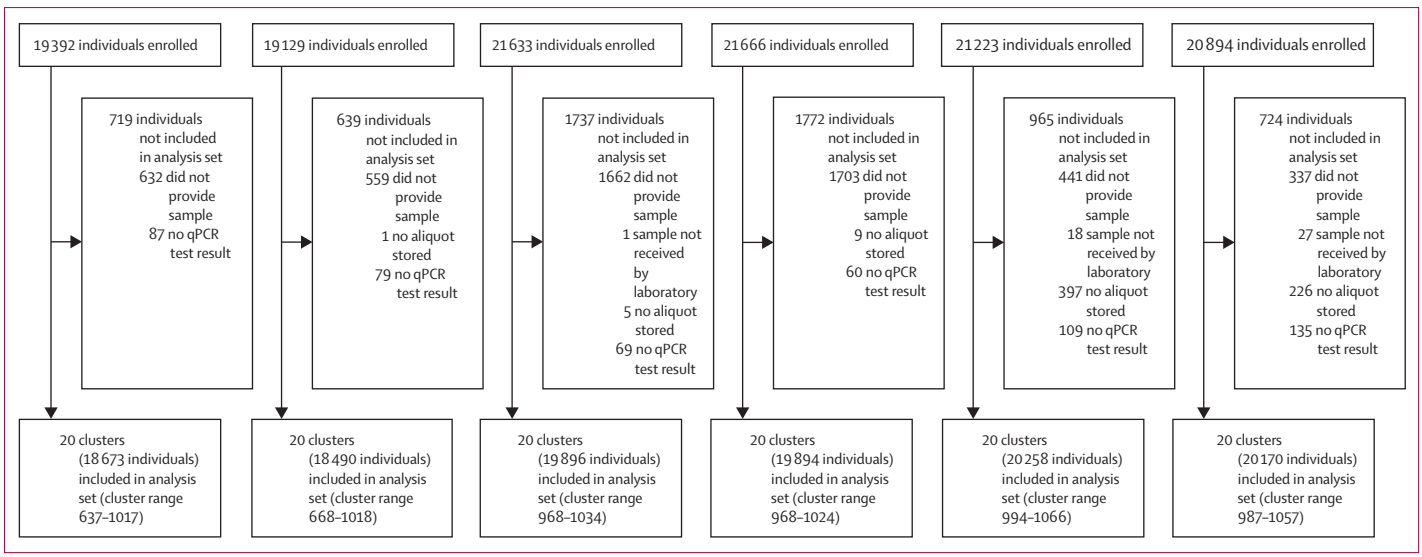


***Figure 1:*** **Trial profile**
MDA=mass drug administration. qPCR=quantitative PCR. *Denominators vary because MDA depends on the national guidelines in each country, with exclusions of anyone younger than 1 year, anyone in their first trimester of pregnancy, and anyone who died between the time of the census and treatment delivery.

any soil-transmitted helminth was analysed in the same manner. A prespecified exploratory analysis assessed cluster-level correlates of transmission interruption in the intervention group using modified Poisson regression.

Post-hoc descriptive subgroup analyses compared the unweighted prevalence of each soil-transmitted helminth species by timepoint, study randomisation group, and participant age.

### Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

## Results

Data collection took place between Oct 10, 2017, and Feb 17, 2023. 357 716 individuals were enumerated in the baseline census and formed the population from which 40 clusters per site were identified and randomly assigned for the trial (figure 1). The sites ranged in geographical size from 148 km² (Benin) to 477 km² (India) and in baseline population from 94 969 to 140 929 individuals. Baseline demographics were similar between treatment groups (table 1). No clusters declined to participate or were lost to follow-up after randomisation. Age-weighted, sex-weighted, and cluster-weighted baseline prevalence was calculated from participants with a valid stool qPCR result and age and sex data available (10 045 in Benin, 9995 in India, and 9940 in Malawi), and was 10·6% (95% CI 10·1–11·2) in Benin, 29·9% (29·0–30·8) in India, and 13·7% (13·1–14·4) in Malawi, driven primarily by *N americanus* infections at all sites. 157 individuals (71 in the control group and 86 in the intervention group) were identified with moderate or heavy-intensity infection by the Kato–Katz technique at baseline and were treated with a single dose of albendazole in schools or by the study team.

In the intervention group, community-wide MDA coverage was high at all sites across the six rounds, ranging from 40 032 (82·4%) of 48 564 to 41 993 (92·0%) of 45 637 in Benin, 46 083 (78·9%) of 58 042 to 55 738 (92·1%) of 60 518 in Malawi, and 63 0088 (1·7%) of 77 096 to 70 339 (95·2%) of 73 924 in India (figure 1; appendix 1 p 6). Coverage of directly observed therapy ranged from 35 296 (75·1%) of 47 005 to 40 873 (91·1%) of 44 890 in Benin, 32 538 (68·6%) of 47 412 to 55 198 (91·6%) of 60 235 in Malawi, and 61 422 (80·1%) of 76 704 to 53 861 (89·8%) of 59 963 in India. Some rounds had higher denominators because those already treated in school were excluded and no school-based deworming was delivered in some cases (rounds 1, 3, and 5 in Malawi and Benin due to national policies and rounds 5 and 6 in India due to the COVID-19 pandemic). Treatment uptake among individuals reached during door-to-door MDA exceeded 90% at all sites and rounds (data not shown).

Baseline and endline weighted prevalence of *N americanus* in each cluster are displayed in figure 2. After 3 years (six rounds) of intervention followed by 24 months during which no deworming was provided, mean cluster-specific age-weighted and sex-weighted prevalence of *N americanus* decreased in all sites in both groups (in Benin from 7·2% [SD 7·1] to 4·0% [4·1] in the control group and 7·2% [7·7] to 1·8% [1·9] in the intervention group; in India from 29·3% [14·9] to 22·0% [15·0] in the control group and 28·6% [17·4] to 9·8% [11·3] in the intervention group; and in Malawi

| | Benin | | India | | Malawi | |
|---|---|---|---|---|---|---|
| | School-based deworming | Community-wide MDA | School-based deworming | Community-wide MDA | School-based deworming | Community-wide MDA |
| **Study site characteristics** | | | | | | |
| Geographical area of study site, km² | 84·5 | 63·8 | 285·2 | 289·5 | 140·3 | 148·3 |
| Urbanicity in study clusters* | | | | | | |
| Rural | 9 (45·0%) | 9 (45·0%) | 17 (85·0%) | 16 (80·0%) | 16 (80·0%) | 15 (75·0%) |
| Peri-urban | 4 (20·0%) | 4 (20·0%) | 3 (15·0%) | 4 (20·0%) | 4 (20·0%) | 5 (25·0%) |
| Urban | 7 (35·0%) | 7 (35·0%) | 0 | 0 | 0 | 0 |
| **Household characteristics** | | | | | | |
| Households enumerated | 11 905 | 12 473 | 18 716 | 17 819 | 13 762 | 13 988 |
| Household residents† | 4 (2–5) | 4 (2–5) | 4 (3–5) | 4 (3–5) | 4 (3–6) | 4 (3–6) |
| Population density within 0·5 km of the household | | | | | | |
| <1000 people per km² | 2098 (17·6%) | 2650 (21·2%) | 9729 (52·0%) | 8694 (48·8%) | 5848 (42·5%) | 4098 (29·3%) |
| 1000–4999 people per km² | 6733 (56·6%) | 5003 (40·1%) | 8084 (43·2%) | 8715 (48·9%) | 7914 (57·5%) | 9890 (70·7%) |
| ≥5000 people per km² | 3074 (25·8%) | 4820 (38·6%) | 903 (4·8%) | 410 (2·3%) | 0 | 0 |
| Owner-occupied dwelling | 7369 (61·9%) | 7720 (61·9%) | 16 703 (89·2%) | 15 928 (89·4%) | 11 769 (85·5%) | 12 195 (87·2%) |
| Flooring material | | | | | | |
| Natural | 2086 (17·5%) | 2213 (17·7%) | 2413 (12·9%) | 2151 (12·1%) | 10 847 (78·8%) | 11 229 (80·3%) |
| Manmade | 9784 (82·2%) | 10 192 (81·7%) | 16 284 (87·0%) | 15 647 (87·8%) | 2905 (21·1%) | 2751 (19·7%) |
| Other or unknown | 35 (0·3%) | 68 (0·5%) | 19 (0·1%) | 21 (0·1%) | 10 (0·1%) | 8 (0·1%) |
| Sanitation‡ | | | | | | |
| Basic facilities | 2835 (23·8%) | 2838 (22·8%) | 6200 (33·1%) | 5473 (30·7%) | 9367 (68·1%) | 9515 (68·0%) |
| Limited facilities | 3297 (27·7%) | 3430 (27·5%) | 359 (1·9%) | 294 (1·6%) | 3492 (25·4%) | 3478 (24·9%) |
| Unimproved facilities | 1142 (9·6%) | 1300 (10·4%) | 186 (1·0%) | 254 (1·4%) | 534 (3·9%) | 659 (4·7%) |
| No facilities (open defecation) | 4388 (36·9%) | 4636 (37·2%) | 11 954 (63·9%) | 11 792 (66·2%) | 352 (2·6%) | 305 (2·2%) |
| Other or unknown | 243 (2·0%) | 269 (2·2%) | 17 (0·1%) | 6 (<0·1%) | 17 (0·1%) | 31 (0·2%) |
| Drinking water source‡ | | | | | | |
| Basic | 9967 (83·7%) | 10 197 (81·8%) | 17 328 (92·6%) | 16 553 (92·9%) | 10 524 (76·5%) | 10 271 (73·4%) |
| Limited | 688 (5·8%) | 865 (6·9%) | 631 (3·4%) | 512 (2·9%) | 2970 (21·6%) | 3513 (25·1%) |
| Unimproved | 1196 (10·0%) | 1357 (10·9%) | 616 (3·3%) | 634 (3·6%) | 241 (1·8%) | 170 (1·2%) |
| Surface water | 20 (0·2%) | 17 (0·1%) | 49 (0·3%) | 30 (0·2%) | 26 (0·2%) | 27 (0·2%) |
| Other or unknown | 34 (0·3%) | 37 (0·3%) | 92 (0·5%) | 90 (0·5%) | 1 (<0·1%) | 7 (0·1%) |
| Household has electricity | 5253 (44·1%) | 5493 (44·0%) | 17 581 (93·9%) | 16 615 (93·2%) | 786 (5·7%) | 541 (3·9%) |
| Household has livestock | 1687 (14·2%) | 1488 (11·9%) | 7580 (40·5%) | 6872 (38·6%) | 4871 (35·4%) | 4858 (34·7%) |
| Household has a mobile phone | 8889 (74·7%) | 9012 (72·3%) | 15 688 (83·8%) | 15 004 (84·2%) | 6032 (43·8%) | 5965 (42·6%) |
| **Study population** | | | | | | |
| Enumerated | 46 728 | 48 241 | 72 472 | 68 457 | 60 811 | 61 007 |
| Sex | | | | | | |
| Male | 22 700 (48·6%) | 23 188 (48·1%) | 36 141 (49·9%) | 34 153 (49·9%) | 28 589 (47·0%) | 28 892 (47·4%) |
| Female | 24 028 (51·4%) | 25 052 (51·9%) | 36 318 (50·1%) | 34 300 (50·1%) | 32 218 (53·0%) | 32 114 (52·6%) |
| Other | 0 | 1 (<0·1%) | 13 (<0·1%) | 4 (<0·1%) | 4 (<0·1%) | 1 (<0·1%) |
| Age distribution | | | | | | |
| Infants (<1 year) | 1297 (2·8%) | 1319 (2·7%) | 900 (1·2%) | 850 (1·2%) | 2199 (3·6%) | 2168 (3·6%) |
| Preschool-age children (1–4 years) | 5413 (11·6%) | 5775 (12·0%) | 4453 (6·1%) | 4029 (5·9%) | 8768 (14·4%) | 8687 (14·2%) |
| School-age children (5–14 years) | 12 897 (27·6%) | 13 146 (27·3%) | 11 260 (15·5%) | 10 578 (15·5%) | 18 905 (31·1%) | 18 747 (30·7%) |
| Adults (≥15 years) | 26 919 (57·6%) | 27 963 (58·0%) | 55 859 (77·1%) | 53 000 (77·4%) | 30 840 (50·7%) | 31 321 (51·3%) |
| Women of reproductive age (15–49 years) | 10 388 (22·2%) | 10 876 (22·5%) | 20 180 (27·8%) | 19 098 (27·9%) | 13 720 (22·6%) | 13 702 (22·5%) |
| Age unknown | 202 (0·4%) | 38 (0·1%) | 0 | 0 | 99 (0·2%) | 84 (0·1%) |

(Table 1 continues on next page)

| | Benin | | India | | Malawi | |
|---|---|---|---|---|---|---|
| | School-based deworming | Community-wide MDA | School-based deworming | Community-wide MDA | School-based deworming | Community-wide MDA |
| (Continued from previous page) | | | | | | |
| School attendance among school-age children | | | | | | |
| Attending school | 10 070/12 897 (78·1%) | 9961/13 146 (75·8%) | 10 560/11 260 (93·8%) | 10 033/10 578 (94·8%) | 16 953/18 905 (89·7%) | 16 819/18 747 (89·7%) |
| Not attending school | 1705/12 897 (13·2%) | 1805/13 146 (13·7%) | 697/11 260 (6·2%) | 545/10 578 (5·2%) | 1934/18 905 (10·2%) | 1908/18 747 (10·2%) |
| Unknown | 1122/12 897 (8·7%) | 1380/13 146 (10·5%) | 3/11 260 (<0·1%) | 0 | 18/18 905 (0·1%) | 20/18 747 (0·1%) |
| Highest level of education among adults aged ≥20 years | | | | | | |
| No education or less than primary school | 8122/22 554 (36·0%) | 8124/23 430 (34·7%) | 16 669/49 579 (33·6%) | 15 576/47 031 (33·1%) | 9927/24 300 (40·9%) | 10 352/24 790 (41·8%) |
| Primary school incomplete or complete | 4094/22 554 (18·2%) | 4344/23 430 (18·5%) | 14 988/49 579 (30·2%) | 14 215/47 031 (30·2%) | 10 887/24 300 (44·8%) | 11 283/24 790 (45·5%) |
| Secondary school incomplete or complete | 3589/22 554 (15·9%) | 3691/23 430 (15·8%) | 8572/49 579 (17·3%) | 8180/47 031 (17·4%) | 2440/24 300 (10·0%) | 2149/24 790 (8·7%) |
| Above secondary school | 4119/22 554 (18·3%) | 4081/23 430 (17·4%) | 9104/49 579 (18·4%) | 8812/47 031 (18·7%) | 66/24 300 (0·3%) | 42/24 790 (0·2%) |
| Other or unknown | 2630/22 554 (11·7%) | 3190/23 430 (13·6%) | 246/49 579 (0·5%) | 248/47 031 (0·5%) | 980/24 300 (4·0%) | 964/24 790 (3·9%) |
| Ethnicity§ | | | | | | |
| Majority language | 41 669 (89·2%) | 43 104 (89·4%) | 69 974 (96·6%) | 66 263 (96·8%) | 57 953 (95·3%) | 58 663 (96·1%) |
| Minority language | 5031 (10·8%) | 5122 (10·6%) | 2487 (3·4%) | 2194 (3·2%) | 2854 (4·7%) | 2371 (3·9%) |
| Unknown | 28 (0·1%) | 15 (<0·1%) | 11 (<0·1%) | 0 | 4 (<0·1%) | 3 (<0·1%) |
| Migration¶ | | | | | | |
| Lived outside the household most of the past year | 701/22 554 (1·5%) | 715/23 430 (1·5%) | 1812/49 579 (2·5%) | 1976/47 031 (2·9%) | 2287/24 300 (3·8%) | 2342/24 790 (3·8%) |
| Slept elsewhere the night before the census | 1318/22 554 (2·8%) | 1232/23 430 (2·6%) | 3963/49 579 (5·5%) | 3816/47 031 (5·6%) | 3354/24 300 (5·5%) | 3387/24 790 (5·6%) |
| **Baseline quantitative PCR prevalence estimates‖** | | | | | | |
| Unweighted | | | | | | |
| Any soil-transmitted helminth | 477/5010 (9·5%) | 488/5035 (9·7%) | 1302/5013 (26·0%) | 1300/4982 (26·1%) | 589/4838 (12·2%) | 656/5102 (12·9%) |
| *N americanus* | 347/5010 (6·9%) | 349/5035 (6·9%) | 1291/5013 (25·8%) | 1287/4982 (25·8%) | 576/4838 (11·9%) | 652/5102 (12·8%) |
| *A duodenale* | 0/5010 | 2/5035 (<0·1%) | 8/5013 (0·2%) | 9/4982 (0·2%) | 15/4838 (0·3%) | 6/5102 (0·1%) |
| *A lumbricoides* | 142/5010 (2·8%) | 136/5035 (2·7%) | 4/5013 (0·1%) | 4/4982 (0·1%) | 2/4838 (<0·1%) | 1/5102 (<0·1%) |
| *T trichiura* | 10/5010 (0·2%) | 9/5035 (0·2%) | 9/5013 (0·2%) | 8/4982 (0·2%) | 4/4838 (0·1%) | 2/5102 (<0·1%) |
| Weighted** | | | | | | |
| Any soil-transmitted helminth | 10·7% (9·9–11·6) | 10·5% (9·7–11·4) | 29·5% (28·3–30·8) | 30·3% (29·0–31·6) | 13·2% (12·2–14·3) | 14·3% (13·3–15·4) |
| *N americanus* | 8·2% (7·5–9·1) | 7·8% (7·1–8·5) | 29·3% (28·0–30·6) | 30·0% (28·7–31·3) | 12·9% (11·9–14·0) | 14·2% (13·2–15·3) |
| *A duodenale* | 0 | 0·1% (0·0–0·2) | 0·2% (0·1–0·3) | 0·2% (0·1–0·4) | 0·4% (0·2–0·7) | 0·1% (0·0–0·2) |
| *A lumbricoides* | 2·8% (2·4–3·3) | 2·7% (2·4–3·3) | 0·1% (0·0–0·2) | 0·1% (0·0–0·1) | <0·1% (0·0–0·1) | <0·1% (0·0–0·1) |
| *T trichiura* | 0·2% (0·1–0·5) | 0·2% (0·1–0·3) | 0·2% (0·1–0·4) | 0·1% (0·1–0·3) | 0·1% (0·0–0·3) | <0·1% (0·0–0·2) |

Data are n, n (%), or n/N (%) unless otherwise specified. *A duodenale=Ancylostoma duodenale. A lumbricoides=Ascaris lumbricoides.* MDA=mass drug administration. *N americanus=Necator americanus. T Trichiura=Trichuris trichuria.* *As defined by each study team. 20 clusters per intervention group. †Median (IQR). ‡ As defined by the WHO–UNICEF Joint Monitoring Programme for Water Supply, Sanitation, and Hygiene 2018.[16] § Majority language is defined as Pedah, Sahouè, Watchi, Mina, Adja, and Xwla in Benin, Tamil in India, and Chiyao in Malawi. Minority language is defined as Fon or other language in Benin, Hindi, Telegu, Urdu, or other language in India, and Chichewa or other language in Malawi. ¶Column does not sum to total as respondents could report living outside of the household, sleeping elsewhere, or neither. ‖Prevalence as measured by quantitative PCR from the baseline prevalence survey. Soil-transmitted helminth positivity defined as a cycle threshold <34·43980 for *N americanus*, <28·57587 for *A lumbricoides*, and <40·00 for *A duodenale* and *T trichiura*. **Prevalence estimates (95% CIs) weighted to match the age, sex, and cluster distribution of the census.

***Table 1:*** **Characteristics of participants at baseline**

from 13·6% [5·6] to 10·0% [3·6] in the control group and 14·5% [5·2] to 4·1% [1·4] in the intervention group; appendix 1 p 13). After adjustment, compared with the control group, the prevalence of *N americanus* in the intervention group at endline was 56% lower (prevalence ratio 0·44 [95% CI 0·34–0·58]; p<0·0001) in Benin, 59% lower (0·41 [0·32–0·52]; p<0·0001) in India, and 60% lower (0·40 [0·34–0·46]; p<0·0001) in Malawi. In the analysis that pooled all sites, prevalence was 59% lower in the intervention group than the control group (0·41 [0·36–0·48]; p<0·0001) with no effect modification observed by site (p=0·51). The prevalence of any soil-transmitted helminth species in the intervention group at endline was 48% lower in Benin, 59% lower in India, and 60% lower in Malawi than in the control group (p<0·0001 for all comparisons) with a pooled reduction of 58% (p<0·0001) and no effect modification by site (p=0·24; table 2). Greater reductions in prevalence

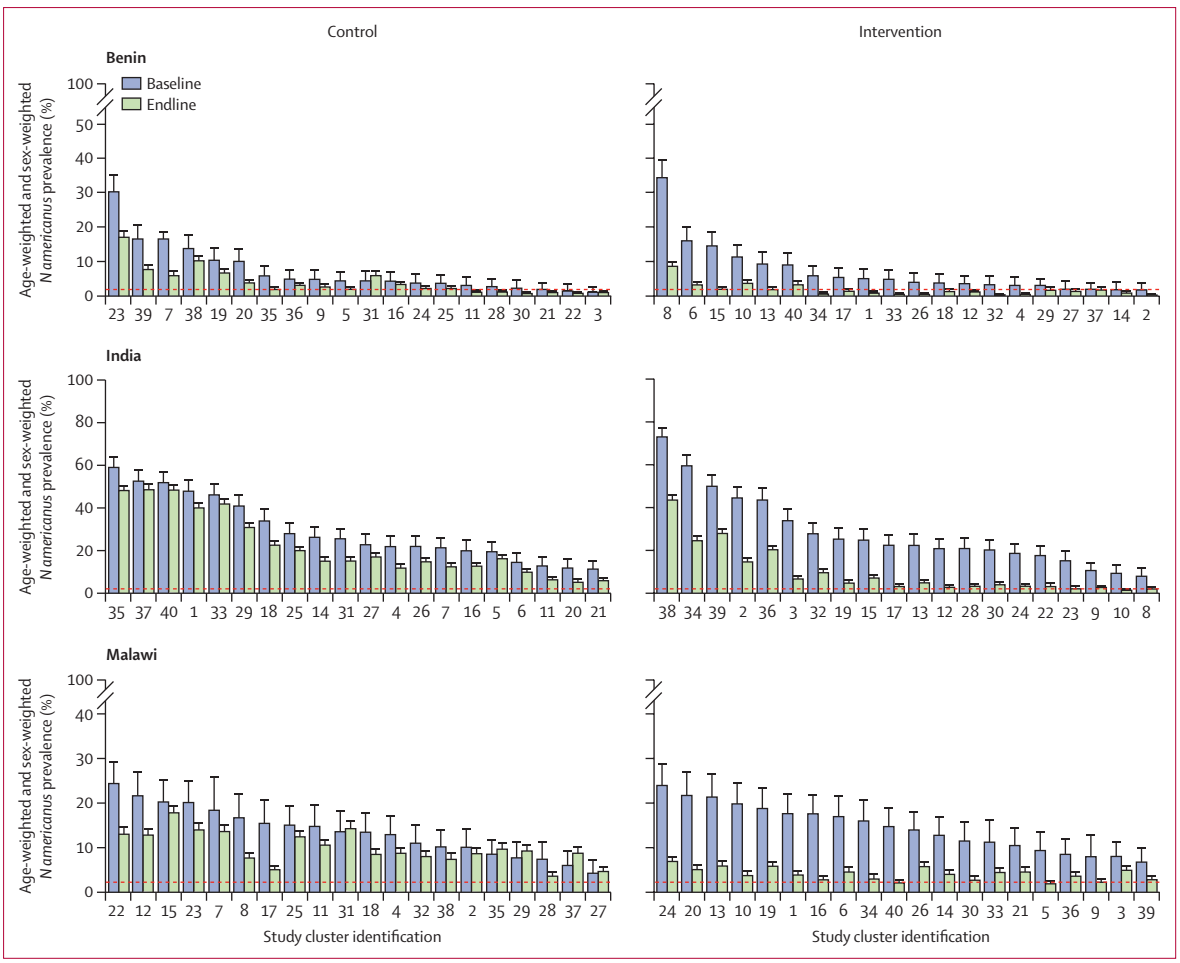


***Figure 2:*** **Baseline and endline individual-level *N americanus* qPCR prevalence for each cluster, by treatment group and country**
*N americanus* qPCR prevalence was computed for each study cluster at baseline (mean 403 [SD 34] samples per cluster) and endline (978 [80] samples per cluster) weighted to the age distribution and sex distribution of the most recent census at the time of survey. Clusters have been ordered by prevalence at baseline (highest to lowest). Error bars represent one-sided binomial 95% CIs and prevalences are displayed separated by site and study treatment group with an overlaid transmission interruption threshold (≤2%). The y axes are presented to different scales per country to enable better visualisation of the data. *N americanus*=*Necator americanus*. qPCR=quantitative PCR.

of all soil-transmitted helminth species combined were observed in the community-wide MDA group than the school-based deworming group at all three sites; however, no significant differences in the prevalence of specific species other than *N americanus* (ie, *A duodenale, A lumbricoides,* and *T trichiura*) between groups at any of the sites were found. In subgroup analyses of preschool-aged children, school-aged children, women of reproductive age, and all adults, greater reductions were also observed in the community-wide MDA group than the school-based deworming group in all descriptive analyses across all sites, with the exception of preschool-aged children in Malawi (appendix 1 p 14).

At endline, transmission interruption was achieved for the predominant soil-transmitted helminth species (*N americanus)* in 17 (43%) of 40 clusters in Benin (11 [55%] of 20 clusters in the intervention group *vs* six [15%] of 20 clusters in the control group, p=0·20), in one (5%) of 20 intervention clusters versus none of 20 clusters in the control group in India (p=1·00), and in no clusters in either group in Malawi (p=1·00; appendix 1 p 15). Transmission interruption of all soil-transmitted helminths species was achieved in 14 (35%) of 40 clusters in Benin (nine [45%] of 20 clusters in the intervention group *vs* five [25%] of 20 clusters in the control group, p=0·32) and in no clusters in India or Malawi. Clusters that achieved transmission interruption had lower baseline prevalence than those that did not in both control and intervention groups; in Benin, the 11 clusters achieving interruption of *N americanus* in the intervention group had a higher baseline point prevalence of *N americanus* (median 3·6% [IQR 2·5–4·4], mean 3·5% [SD 1·4]) compared with the six clusters achieving *N americanus* interruption in the control group (median 2·1% [1·5–2·6], mean 2·1% [0·8]; appendix 1 p 16).

| | Benin | | | India | | | Malawi | | | Pooled | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Control (n=18 673) | Intervention (n=18 490) | p value* | Control (n=19 896) | Intervention (n=19 894) | p value* | Control (n=20 258) | Intervention (n=20 170) | p value* | Control (n=58 827) | Intervention (n=58 554) | p value* |
| ***N americanus*** | | | | | | | | | | | | |
| Endline prevalence† | 748 (4·0%) | 322 (1·7%) | .. | 4310 (21·7%) | 1906 (9·8%) | .. | 1989 (9·8%) | 827 (4·1%) | .. | 7047 (12·0%) | 3055 (5·2%) | .. |
| Treatment effect | 1 (ref) | 0·43 (0·23–0·83) | 0·011 | 1 (ref) | 0·44 (0·25–0·79) | 0·0061 | 1 (ref) | 0·42 (0·34–0·52) | <0·001 | 1 (ref) | 0·43 (0·30–0·63) | <0·001 |
| Adjusted treatment effect‡ | 1 (ref) | 0·44 (0·34–0·58) | <0·001 | 1 (ref) | 0·41 (0·32–0·52) | <0·001 | 1 (ref) | 0·40 (0·34–0·46) | <0·001 | 1 (ref) | 0·41 (0·36–0·48) | <0·001 |
| ***A duodenale*** | | | | | | | | | | | | |
| Endline prevalence† | 11 (0·1%) | 11 (0·1%) | .. | 3 (<0·1%) | 3 (<0·1%) | .. | 15 (0·1%) | 6 (<0·1%) | .. | 29 (0·1%) | 20 (<0·1%) | .. |
| Treatment effect | 1 (ref) | 1·02 (0·37–2·83) | 0·97 | 1 (ref) | 1·00 (0·23–4·39) | >0·99 | 1 (ref) | 0·41 (0·09–1·75) | 0·23 | 1 (ref) | 0·70 (0·34–1·45) | 0·34 |
| Adjusted treatment effect‡ | 1 (ref) | 0·83 (0·27–2·57) | 0·75 | 1 (ref) | 0·92 (0·17–4·94) | 0·92 | 1 (ref) | 0·31 (0·07–1·40) | 0·13 | 1 (ref) | 0·70 (0·33–1·51) | 0·37 |
| ***A lumbricoides*** | | | | | | | | | | | | |
| Endline prevalence† | 59 (0·3%) | 123 (0·7%) | .. | 7 (<0·1%) | 17 (0·1%) | .. | 15 (0·1%) | 12 (0·1%) | .. | 81 (0·1%) | 152 (0·3%) | .. |
| Treatment effect | 1 (ref) | 2·08 (0·49–8·87) | 0·32 | 1 (ref) | 2·44 (0·83–7·14) | 0·10 | 1 (ref) | 0·80 (0·39–1·67) | 0·56 | 1 (ref) | 1·88 (0·59–6·00) | 0·28 |
| Adjusted treatment effect‡ | 1 (ref) | 1·50 (0·83–2·72) | 0·18 | 1 (ref) | 2·07 (0·81–5·29) | 0·13 | 1 (ref) | 0·71 (0·37–1·38) | 0·31 | 1 (ref) | 1·40 (0·89–2·18) | 0·14 |
| ***T trichiura*** | | | | | | | | | | | | |
| Endline prevalence† | 6 (<0·1%) | 13 (0·1%) | .. | 5 (<0·%1) | 7 (<0·1%) | .. | 4 (<0·1%) | 2 (<0·1%) | .. | 15 (<0·1%) | 22 (<0·1%) | .. |
| Treatment effect | 1 (ref) | 2·20 (0·88–5·51) | 0·093 | 1 (ref) | 1·40 (0·38–5·18) | 0·61 | 1 (ref) | 0·50 (0·09–2·81) | 0·43 | 1 (ref) | 1·48 (0·75–2·91) | 0·26 |
| Adjusted treatment effect‡ | 1 (ref) | 2·26 (0·85–6·02) | 0·10 | 1 (ref) | 0·95 (0·34–2·67) | 0·93 | 1 (ref) | 0·28 (0·03–2·63) | 0·27 | 1 (ref) | 1·54 (0·76–3·12) | 0·23 |
| **Any soil-transmitted helminth species** | | | | | | | | | | | | |
| Endline prevalence† | 819 (4·4%) | 467 (2·5%) | .. | 4318 (21·7%) | 1930 (9·7%) | .. | 2016 (10·0%) | 846 (4·2%) | .. | 7153 (12·2%) | 3243 (5·5%) | .. |
| Treatment effect | 1 (ref) | 0·57 (0·31–1·05) | 0·073 | 1 (ref) | 0·45 (0·25–0·80) | 0·0061 | 1 (ref) | 0·42 (0·34–0·52) | <0·001 | 1 (ref) | 0·46 (0·32–0·65) | <0·001 |
| Adjusted treatment effect‡ | 1 (ref) | 0·52 (0·38–0·71) | <0·001 | 1 (ref) | 0·41 (0·33–0·52) | <0·001 | 1 (ref) | 0·40 (0·35–0·47) | <0·001 | 1 (ref) | 0·42 (0·37–0·49) | <0·001 |

Data are prevalence ratio (95% CI) or n (%) unless otherwise specified. For Benin, sample sizes are 37 163 (unadjusted) and 37 058 (adjusted). For India, sample sizes are 39 790 (unadjusted) and 39 598 (adjusted). For Malawi, sample sizes are 40 428 (unadjusted) and 40 294 (adjusted). For pooled countries, sample sizes are 117 381 (unadjusted) and 116 950 (adjusted). *A duodenal=Ancylostoma duodenale. A lumbricoides=Ascaris lumbricoides. N americanus=Necator americanus. T Trichiura=Trichuris trichuria.* *Assessed by estimating prevalence ratios using modified Poisson regression with robust SEs. The primary analysis is the adjusted analysis. †Unweighted; soil-transmitted helminth positivity by quantitative PCR defined as a cycle threshold <34·43980 for *N americanus*, <28·57587 for *A lumbricoides*, and <40·00 for *A duodenale* and *T trichiura* . ‡Adjusted for baseline study cluster-specific age-weighted and sex-weighted prevalence, age distribution, sex, individual migration status, household size, population density per 1000 individuals within 0·5 km of the household, socioeconomic status as measured by an asset index divided into quintiles, and water and sanitation access as measured by WHO–UNICEF Joint Monitoring Programme for Water Supply, Sanitation, and Hygiene indicators.

***Table 2:*** **Comparison of the individual-level soil-transmitted helminth species-specific endline quantitative PCR prevalence**

| | Transmission interrupted (N=11 clusters) | Transmission not interrupted (N=9 clusters) | RR (95% CI)* | p value |
|---|---|---|---|---|
| Baseline prevalence of *N americanus*† | 3·5% (1·4) | 11·6% (9·8) | 0·80 (0·71–0·90) | 0·0003 |
| Population density‡ | 4761·4 (1652·3) | 2493·4 (2021·9) | 1·27 (1·10–1·47) | 0·0011 |
| Households with open defecation§ | 24·0% (32·5) | 49·4% (32·4) | 0·92 (0·83–1·03) | 0·17 |
| Individual MDA treatment coverage in rounds 1–6 | 84·4% (4·2) | 86·5% (5·0) | 0·95 (0·86–1·05) | 0·30 |
| Clusters that achieved mean 90% coverage in rounds 1–6 | 1/11 (9·1%) | 2/9 (22·2%) | 0·57 (0·11–2·95) | 0·50 |
| Individual MDA treatment acceptance¶ | 57·6% (9·8) | 63·7% (10·6) | 0·97 (0·92–1·02) | 0·24 |
| Migration of individuals‖ | 5·0% (2·8) | 4·1% (1·9) | 1·07 (0·94–1·22) | 0·32 |
| Households with earthen household floor materials** | 9·9% (7·1) | 23·4% (10·0) | 0·70 (0·57–0·86) | 0·0007 |

Data are mean (SD) or n/N (%) unless specified. *N americanus*=*Necator americanus*. RR=risk ratio. *All models were modified Poisson regression with robust SEs. †Study cluster-specific *N americanus* prevalence was weighted to the age and sex distribution of the baseline census population. *N americanus* positivity by quantitative PCR was defined as a cycle threshold <34·43980. RR is expressed per 1% increase. ‡The number of study residents living within 0·5 km of each household expressed per km². RR is expressed per 1000 individuals. §RR is expressed per 5% change in open defecation. ¶The percentage of cluster residents who were treated at all MDA rounds in which they were eligible. RR is expressed per 1% increase. ‖Defined as the percentage of cluster residents who reported living in the household less than 6 months in the previous year during the endline census. RR is expressed per 1% increase. **Defined as the percentage of cluster residents who lived in a household with floor materials made from earth, sand, mud, clay, or dung during the endline census. RR is expressed per 5% change in floor material.

***Table 3:*** **Cluster-level factors associated with transmission interruption of *N americanus* in the intervention group in Benin**

Factors associated with transmission interruption of *N americanus* in the intervention group were only assessed for Benin and included baseline age-weighted and sex-weighted cluster prevalence (risk ratio 0·80 [95% CI 0·71–0·90] per 1% increase; p=0·0003), cluster mean population density (1·27 [1·10–1·47] per 1000 individuals per km² within 0·5 km of households; p=0·0011), and percentage of households with earthen flooring material (0·70 [0·57–0·86] per 5% increase; p=0·0007; table 3).

Nearly all adverse events recorded were in the intervention group as they were only passively reported during MDA (the intervention), with the exception of in Malawi, where the Government requested the study team deliver the standard of care during the study. In India and Benin, the Government delivered the standard of care.

Adverse events were not collected disaggregated by group and were not a study outcome that was compared by randomisation group to assess if there were differences between groups (given the large body of evidence showing albendazole is safe). To be conservative and ensure the maximal protection of research subjects, we instructed participants to passively report adverse events and followed up all reports to ensure resolution.

Over the course of the study, 984 adverse events were reported among 487 participants, of which 32 adverse events among 13 participants resulted in hospitalisation and were classified as serious adverse events. There were no deaths and all participants reporting serious adverse events recovered. All but three serious adverse events were considered not related to study procedures.

One serious adverse event in Benin was classified as probably related to study procedures when a woman aged 50 years developed diarrhoea and vomiting leading to fainting and hospitalisation following receipt of MDA. In Malawi, two girls aged 12 years had fainting leading to hospitalisation following school-based deworming administration, which was classified as possibly related to study procedures. Study protocol deviations were tracked and monitored by the data safety and monitoring committee and are presented in the appendix 1 (pp 7–12).

## Discussion

We have shown that achieving transmission interruption of soil-transmitted helminths is not feasible at a programmatically relevant scale using MDA delivered over a 3-year period (based on a prevalence of ≤2% by qPCR measured 2 years after cessation of deworming). Transmission interruption was only achieved in focal geographical areas (the transmission of infection involving individuals residing in close spatial and temporal proximity) and was observed almost exclusively in Benin. Although transmission interruption was achieved in more intervention clusters than control clusters in Benin (11 [55%] of 20 *vs* six [15%] of 20), this difference was not statistically significant. In the intervention group, features associated with urban environments, including improved flooring and high population density, were associated with greater likelihood of achieving *N americanus* transmission interruption. Baseline prevalence was strongly negatively associated with *N americanus* transmission interruption in the intervention group. In the control group, prevalence in clusters that achieved interruption approached the transmission interruption threshold (≤2%) before the start of the trial (appendix 1 p 16). These findings suggest that although it might be biologically feasible to break transmission over six rounds of MDA, it is unlikely to be attained across broad geographical settings within a timeframe of 3 years, even when coverage is exceptionally high. The substantial reductions in prevalence in the community-wide MDA group observed across all sites suggest that a longer period of deworming than that studied in this trial could potentially achieve transmission interruption in more clusters. These results support the current WHO targets of eliminating soil-transmitted helminth infection to a prevalence level where it is no longer a public health problem (defined as <2% prevalence of moderate or heavy-intensity infection) and do not appear to support a shift towards a global soil-transmitted helminth policy targeting transmission interruption.

Importantly, we observed substantially greater reductions in the overall prevalence of all soil-transmitted helminth species (driven by the predominant species *N americanus*) using community-wide MDA as opposed to school-based deworming 24 months following cessation of all deworming, a finding that adds greatly to findings from smaller trials.[14,23,24] These greater reductions in prevalence were observed in all age groups, including among preschool-aged children (other than in Malawi), school-aged children, and women of reproductive age, which are populations that are targeted by most current soil-transmitted helminth guidelines and programmes. However, controversy exists regarding the health benefits of deworming, particularly in populations with low levels of moderate or heavy-intensity infection, and these data do not necessarily imply that community-wide MDA would lead to greater reductions in overall morbidity due to helminth infection.[25]

Strengths of this study include the recruitment of large populations across multiple geographies, thereby increasing the generalisability of these results. In addition, the study achieved exceptionally high validated treatment coverage, suggesting that the failure to achieve transmission interruption in all clusters was not due to inadequate coverage.[26] We also showed the feasibility of establishing a high-throughput qPCR platform for soil-transmitted helminth surveillance that can be used to effectively monitor areas with low prevalence in which performance of microscopy-based diagnostics is suboptimal.[27] However, the study did have some limitations. Prevalence was only assessed 24 months following cessation of MDA and samples collected immediately following the final round of MDA have not yet been tested due to a shortage of resources. As such, the trajectory of prevalence following treatment cannot be accurately established. *N americanus* was the predominant species in all three sites and the effects of community-wide MDA might differ in areas where other species predominate. Additional modelling calculations are needed with improved epidemiological data (including with data from DeWorm3) to establish the veracity of a true prevalence of less than 2% as the threshold for transmission interruption across a wide range of transmission settings for the three major soil-transmitted helminth species.[14,23,28] Such simulation-based studies should also establish a range of confidence bounds on qPCR diagnostic tests using positive predictive values for elimination. Finally, prevalence was markedly reduced in both intervention and control clusters, suggesting potential Hawthorne effects, cross-cluster contamination of treatment, or indirect benefits due to reduced exposure to adults with a soil-transmitted helminth infection or environmental contamination with helminth eggs. As clusters were geographically contiguous, reducing the number of individuals shedding soil-transmitted helminth eggs could reduce the reservoir of eggs in the soil and thereby reduce the incidence of new infection.

There is increasing pressure for national governments to finance and deliver national neglected tropical disease programmes.[29] In addition, there is global interest in further optimising the impact of the global drug donation programme and other philanthropic support. As such, the prospect of soil-transmitted helminth elimination is of interest as a potentially cost-effective means of reducing the overall need for resources to support these programmes over time. Our results, from areas with a predominance of hookworm, suggest that transmission interruption is only feasible in focal geographical areas and is unlikely to be achievable at large scale over a period of 3 years, even with high MDA treatment coverage. As a result, elimination of soil-transmitted helminths in most low-income settings does not appear feasible in the timeline tested in this trial. Resources will need to be allocated to allow national programmes to ensure continued delivery of anthelmintics, maintain surveillance, improve coverage, and more effectively integrate MDA with broader health, WASH, and education services. The substantially greater reductions in population prevalence observed with community-wide MDA compared with school-based deworming, deserves careful consideration by neglected tropical disease policy makers given the continued burden of soil-transmitted helminths globally.[30]

#### Contributors

JLW, KHÁ, RB, SSRA, KA, SRG, MI, KK, DTJL, AJFL, ARM, WEO, RP, and KKT conceptualised this Article SRG, SSRA, KHA, RB, GC, EA, KEH, PH, MI, GJI, KK, HL, AJFL, MM, ARM, WEO, NP, RP, KKT, and SAW contributed to data curation. KHÁ, SRG, PH, EA, GJI, MM, ARM, NP, RP, KKT, and JLW did formal analyses of the data. SRG and KKT double coded and verified the reported data. SSRA, KHÁ, RB, MI, KK, DTJL, AJFL, AM, ARM, RP, SAW, and JLW contributed to supervision of the overall trial conduct and analyses. All authors contributed to writing the original draft and contributed equally to investigation, methodology, review, and editing. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. All authors have seen and approved the final manuscript.

#### Declaration of interests

We declare no competing interests.

#### Data sharing

The DeWorm3 datasets, data dictionaries, statistical analysis plan, and study protocol were made publicly available on the Vivli repository in November, 2024. The datasets were anonymised by a third-party vendor. Access to the data and supporting documents is available on request at vivli.org and requires the execution of a Data Use Agreement.

For the **data and supporting documents** see https://doi.org/10.25934/PR00010754

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