Differential effect of mass deworming and targeted deworming for soil-transmitted helminth control in children: a systematic review and meta-analysis

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Summary

Background **Soil-transmitted helminth infections are a major global health issue, causing substantial morbidity in the world's poorest populations. Regular delivery of anthelmintic drugs is the mainstay for global soil-transmitted helminth control. Deworming campaigns are often targeted to school-aged children, who are at high risk of soil-transmitted-helminth-associated morbidity. However, findings from modelling studies suggest that deworming campaigns should be expanded community-wide for effective control of soil-transmitted helminth transmission. We aimed to do a systematic review and meta-analysis to compare the effect of mass (community-wide) and targeted (children only) anthelmintic delivery strategies on soil-transmitted helminth prevalence in school-aged children.**

Methods **In this systematic review and meta-analysis, we searched MEDLINE, Embase, and Web of Science for articles published on or before Nov 5, 2015, reporting soil-transmitted helminth prevalence before and after distribution of albendazole or mebendazole, either targeted to children or delivered to the whole community. We excluded studies in which drug delivery was restricted to infected individuals or to a subset of the community or school, or if follow-up time was less than 3 months or greater than 18 months after drug delivery. We extracted data on study year, country, drug administration strategy, drug dose, number of deworming rounds, treatment coverage, diagnostic method, follow-up interval, and soil-transmitted helminth prevalence before and after treatment. We used inverse variance weighted generalised linear models, with prevalence reduction as the outcome variable, to examine the effect of mass versus targeted drug administration, as well as baseline prevalence, number of drug doses, and follow-up time. This study is registered with PROSPERO, number CRD42016026929.**

Findings **Of 10 538 studies identified, 56 studies were eligible for the systematic review and 38 of these were included in meta-analysis. Results of the regression models showed that mass deworming led to a significantly greater reduction in prevalence in children than targeted deworming, for both hookworm (odds ratio 4·6, 95% CI 1·8–11·6; p=0·0020) and *Ascaris lumbricoides* (16·4, 2·1–125·8; p=0·0092), with no effect seen for *Trichuris trichiura*. There was significant heterogeneity across studies; for targeted studies I^2 was 97% for *A lumbricoides* and hookworm, and 96% for *T trichiura*, and for mass studies, I^2 was 89% for *A lumbricoides*, 49% for hookworm, and 66% for *T trichiura*.**

Interpretation **The results of this meta-analysis suggest that expanding deworming programmes community-wide is likely to reduce the prevalence of soil-transmitted helminths in the high-risk group of school-aged children, which could lead to improved morbidity outcomes. These findings are in support of recent calls for re-evaluation of global soil-transmitted helminth control guidelines.**

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Introduction

Infection with the soil-transmitted helminths, roundworms (*Ascaris lumbricoides*), hookworms (*Ancylostoma duodenale* and *Necator americanus*), and whipworms (*Trichuris trichiura*), is the most common parasitic human disease worldwide, with an estimated 1·45 billion individuals infected.[1] Chronic infection with soil-transmitted helminths can lead to impaired physical and cognitive development, which is of particular concern in school-aged children, who have the highest burden of *A lumbricoides* and *T trichiura* infections and are at high risk of hookworm-associated morbidity.[2,3] Overall, soil-transmitted helminth infection is estimated to cause more than 3 million disability-adjusted life-years worldwide.[4]

The benzimidazole anthelmintics albendazole and mebendazole are the mainstay of treatment for the reduction of disease prevalence and burden.[2] These drugs have excellent safety records;[5] both drugs have high efficacy against *A lumbricoides*, albendazole is efficacious against hookworm, and both drugs are less efficacious against *T trichiura*.[6] Regular repeated treatment is necessary because reinfection can occur rapidly after treatment.[7] As such, soil-transmitted helminth control programmes consist of annual or biannual distribution of anthelmintic drugs to at-risk populations, in accordance with WHO guidelines.[5,8]

Given the high burden of soil-transmitted-helminth-associated morbidity in children, large-scale anthelmintic

Research in context

Evidence before this study

Regular distribution of deworming medications albendazole or mebendazole is the mainstay of control for soil-transmitted helminth infections. Deworming campaigns for soil-transmitted helminth control are typically targeted to school-aged children, who have the highest burden of morbidity. However, mathematical modelling and cost-effectiveness studies have advocated for the expansion of large-scale deworming programmes to all community members. We searched MEDLINE, Embase, and Web of Science to identify articles published in any language before November, 2015, and included papers reporting soil-transmitted helminth prevalence before and after distribution of albendazole or mebendazole, either targeted to children or deliverved to the whole community. Many studies were identified, but none have been synthesised in a systematic review and meta-analysis.

Added value of this study

To our knowledge, this systematic review and meta-analysis is the first to synthesise existing literature reporting the effect of either targeted or mass distribution of deworming medications on the prevalence of soil-transmitted helminth infections in children. Our findings suggest that for both *Ascaris lumbricoides* and hookworm, mass treatment programmes have a greater effect on prevalence reduction than targeted treatment programmes.

Implications of all the available evidence

The results of this meta-analysis contribute to the evidence base surrounding the benefits of expanding drug therapy programmes for control of soil-transmitted helminths to all members of the community. Our findings support those of modelling and cost-effectiveness studies. We suggest that soil-transmitted helminth control guidelines should be re-evaluated with consideration of expansion to community-wide drug administration in endemic areas.

distribution programmes typically focus on targeted delivery to school-aged children (aged 5–14 years).[5] Current WHO guidelines also suggest delivery of anthelmintics to preschool-aged children (aged 2–4 years), women of childbearing age, and people in high-risk occupations (eg, tea pickers).[5,9] In 2012, the London Declaration on Neglected Tropical Diseases announced a cross-sectoral commitment to help eliminate or control preventable neglected tropical diseases by 2020, inspired by WHO roadmap targets.[10] This commitment included a goal of treating 75% of children at risk of soil-transmitted helminth infection in all endemic countries. To this end, 600 million doses of albendazole and mebendazole are donated annually by pharmaceutical companies, enough to treat nearly 70% of the 876 million at-risk children worldwide.[11]

Since this resolution, demand for government-led, school-based deworming programmes has increased worldwide.[12,13] Using school-based infrastructure for anthelmintic delivery is considered a practical and cost-effective method of reaching a large proportion of the population at high risk of soil-transmitted-helminth-associated morbidity,[14] and some evidence has suggested collateral benefits to other age groups in the community, owing to reduced transmission within the population.[15,16]

Interest in the optimal design of soil-transmitted helminth control programmes has increased over the past 5 years. Mathematical modelling has been used to explore the effect of anthelmintic drug therapy on transmission and worm burden in the host population. Results suggest that, in many settings, child-targeted programmes might have limited effect on overall transmission in the community, and that deworming campaigns should be expanded to all age groups.[17–23] Furthermore, findings from cost-effectiveness modelling studies show that community-wide approaches are highly cost-effective;[21] particularly for hookworm,[23] for which adults can act as substantial reservoirs of infection.

Many published studies have investigated the effectiveness of anthelmintic delivery programmes.[7] However, to our knowledge, no comparison of studies has examined mass and targeted delivery strategies (panel). To fill this gap in the literature, this systematic review and meta-analysis aimed to describe existing literature reporting the effects of mass or targeted administration of albendazole or mebendazole on soil-transmitted helminth prevalence in school-aged children, and to examine the differential effects of mass and targeted drug delivery on soil-transmitted helminth prevalence in school-aged children.

Methods

Search strategy and selection criteria

This systematic review and meta-analysis was done according to PRISMA guidelines.[24] Eligible papers were published studies that reported soil-transmitted helminth prevalence before and after mass or targeted delivery of albendazole or mebendazole. Studies that examined other control strategies in addition to anthelmintic drug therapy, including water, sanitation, and hygiene (WASH) improvements, and medications for other neglected tropical diseases (eg, schistosomiasis and lymphatic filariasis) were included. Randomised trials were included if randomisation occurred at the community level or school level, rather than at the household or individual level.

Studies were excluded if anthelmintic delivery was restricted to infected individuals, a random selection of the population, or a specific group of students in a school; if positive cases were re-treated shortly after

initial drug administration; if soil-transmitted helminth prevalence before and after drug administration was not available; if follow-up time was less than 3 months or greater than 18 months; or if albendazole or mebendazole were not used.

The following additional exclusion criteria were applied for the purposes of meta-analysis: number of doses or follow-up time was not reported; different parasitological diagnostic methods were used at baseline and follow-up; data were combined for mass and targeted distribution strategies, several different dosing schedules, or several different follow-up periods; initial prevalence was less than 5%; or time between baseline assessment and first anthelmintic distribution was more than 12 months.

We searched MEDLINE, Embase, and Web of Science on Nov 5, 2015, with no limitations on year or language of publication. We used the following search terms that related to soil-transmitted helminth infection: "helminth" or "soil-transmitted helminth" or "STH" or "nematode" or "geohelminth" or "hookworm" or "roundworm" or "whipworm" or "Trichuris" or "Ascaris" or "Ancylostoma" or "Necator"; and to intervention: "chemotherapy" or "albendazole" or "mebendazole" or "anthelminthic" or "anthelmintic" or "benzimidazoles" or "deworming" or "mass drug administration". The complete search strategy is provided in the appendix (p 2). We sought further studies by hand-searching reference lists of relevant review papers,[7,25,26] WHO guidelines,[8,9] and included papers.

Potentially relevant studies were imported into EndNote (version X7). Study titles and abstracts were screened by NEC and DW, and full-text papers were retrieved for all candidate studies. Studies published in English were examined by two independent researchers (NEC and SJC), discrepancies were discussed with a third reviewer (SVN), and a consensus reached. Studies published in languages other than English (Chinese, French, Spanish, and Portuguese) were reviewed by researchers fluent in those languages (SVN and DW). All studies were assessed for eligibility against the review protocol. The review protocol is available in PROSPERO, registration number CRD42016026929.

Data extraction and quality assessment

Data were extracted by NEC and DW. Data extracted from eligible papers included study year and country; study population; sample size; drug-delivery strategy (mass or targeted); drug dose, frequency, and number of rounds; treatment coverage; additional interventions; and prevalence of each soil-transmitted helminth before and after drug delivery.

If more than one drug regimen was reported in the same study, data were extracted for each regimen separately. Similarly, if multiple populations were examined in the same study (eg, rural and urban), data were extracted for each population separately. In trials with a control group who had drug treatment only, and an intervention group who received an additional intervention (eg, sanitation improvements), only data from the control groups were extracted.

Panel: Mass and targeted drug delivery

WHO defines different modalities of drug therapy, including:

- Mass drug administration: the entire population of an area (eg, state, region, province, district, subdistrict, or village) is given anthelmintic drugs at regular intervals, irrespective of individual infection status
- Targeted drug therapy: specific risk groups in the population, defined by age, sex, or other social characteristic such as occupation (eg, school-aged children, or fishermen) are given anthelmintic drugs at regular intervals, irrespective of individual infection status[8]

In this Article, we use the term mass drug delivery to describe programmes that give anthelmintic drug therapy to all community members, and targeted drug delivery to describe programmes that provide anthelmintic drug therapy only to children.

We contacted 33 authors to request additional information, including age-stratified soil-transmitted helminth prevalence, sample size, drug dose, follow-up time, and treated population. Five authors provided numerical data, which were previously only published in figure format, four authors clarified the treated population, three authors provided sample sizes, two authors clarified drug doses or follow-up time, and two authors provided age-segregated data.

See Online for appendix

We assessed study quality using a scale modified from the validated scale described by Hoy and colleagues,[27] which was designed to assess risk of bias in prevalence studies. Modifications were made to account for most studies being quasi-experimental studies without a control group, consisting of pre-post prevalence surveys. We used the National Heart, Lung, and Blood Institute quality assessment tools for observational cohort and cross-sectional studies,[28] and pre-post design studies,[29] to make these modifications, which included addition of items relating to consistent participant selection and sampling across timepoints, and coverage of the intervention. We assessed studies against nine safeguards, each of which provided additional assurance that there was no bias in the measurement of soil-transmitted helminth prevalence. Both internal and external validity items were included, as suggested for prevalence studies.[27] Quality assessment was done by NEC and cross-checked by SVN, with disagreements resolved through consensus.

For the **study protocol** see http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016026929

Statistical analysis

All analyses were done separately for each soil-transmitted helminth, because of the differences in age distribution, cure and reinfection rates after treatment, and environmental resilience.[2,6,7]

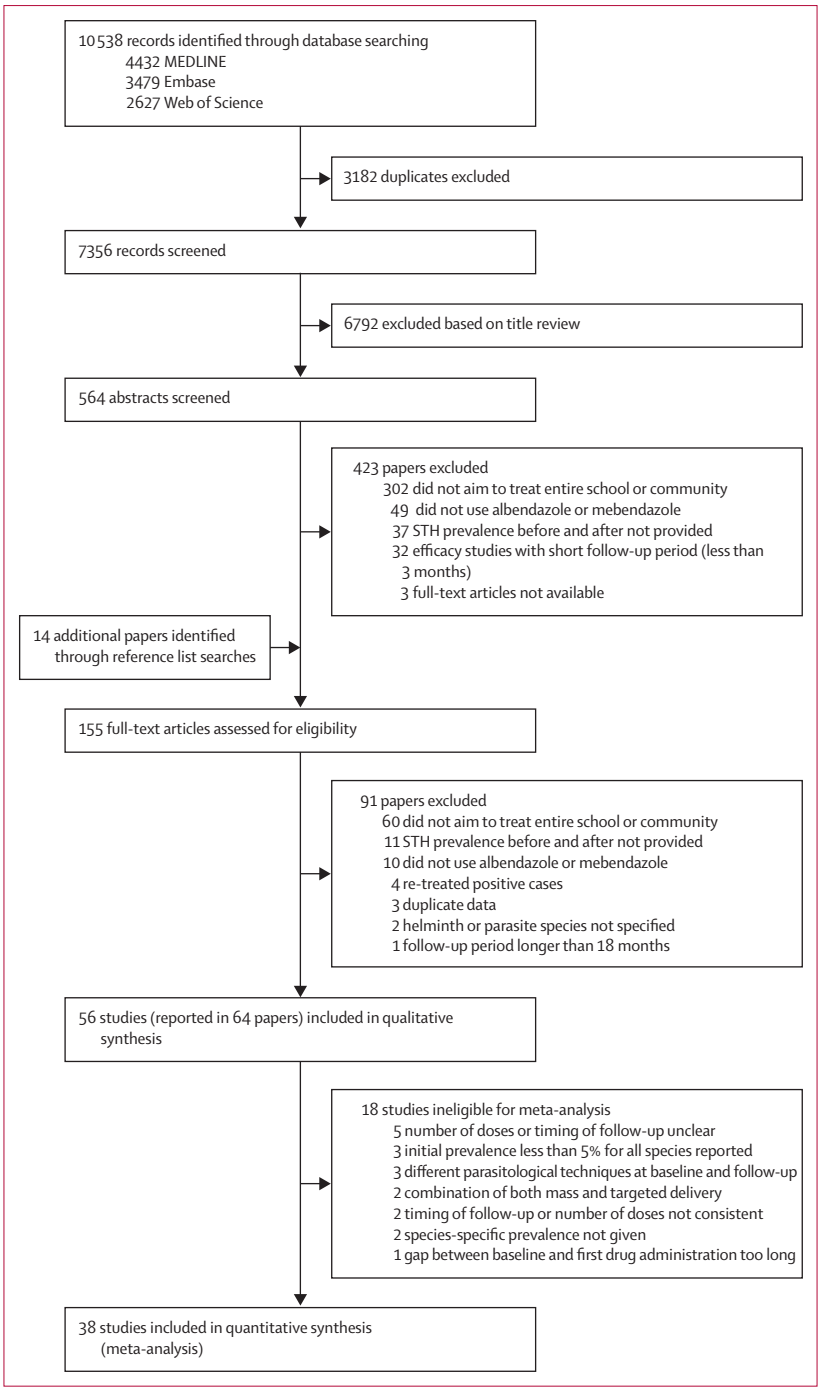

***Figure 1*: Study selection**
STH=soil-transmitted helminth.

Where age-stratified soil-transmitted helminth prevalence was not available (ten studies), we estimated prevalence in school-aged children from community prevalence with scaled age weights[30] and estimates of community age distribution obtained from UN datasets for the relevant country and 5 year period.[31]

The first timepoint at which data were available was considered the baseline. We considered this approach acceptable because soil-transmitted helminth infections rapidly recur after treatment,[7] and many populations in the studies included probably had some previous exposure to anthelmintics.

Given the heterogeneity between studies in terms of number of drug doses, dosing interval, and follow-up period, we used an inverse variance weighted generalised linear model with robust error variances to quantify the effect of these covariates. This regression used the inverse of the variance of each study as weights, so that observations with the least variance provided the most information to the model.

The outcome variable in the model was the prevalence reduction (PReduc). This was defined as $(p_1 - p_2) / p_1 = 1 -$ prevalence ratio, where p_1 is the pre-intervention prevalence proportion and p_2 is the post-intervention prevalence proportion, and p_2/p_1 is the prevalence ratio (PRatio). Only one follow-up prevalence, p_2, was entered per study. In an attempt to achieve consistency, follow-up prevalence was selected as follows: if prevalence was reported after multiple different doses, the assessment closest to the fourth dose was selected; and if prevalence was reported at multiple timepoints after the chosen dose, the assessment closest to 6 months was selected.

PReduc was truncated at its lower boundary so that any prevalence increase was reset to zero; thus, the truncated distribution mirrored that of a proportion. This truncated response variable could then be modelled using a logit link function to linearise it with predicted values.[32] This approach made sense because any increase would be unrelated to the intervention, implying no effect. Coefficients were exponentiated to generate weighted odds ratios based on the study-level predictors.[32] Link specifications were tested using the linktest command in Stata, to assess variance explained by the squared linear predictor.

Due to disproportionately high weights in some studies with very small variances, for the purposes of the weighted regression model, any weights that were more than five times greater than the upper quartile were truncated and replaced with the weight at the threshold. This action stabilised the variance of the regression coefficients and the point estimates.

The following covariates were entered into the model: (1) mass versus targeted distribution; (2) baseline prevalence; (3) number of doses between baseline and follow-up assessments; and (4) follow-up time (months) between most recent dose and prevalence assessment. Cumulative time between first dose and follow-up assessment was co-linear with number of doses, and thus not used. Regression outliers were examined using a leverage against residual squared plot and removed from the analysis.

We did a secondary analysis to synthesise PReduc (non-truncated) for each soil-transmitted helminth. To

	Ascaris lumbricoides	Hookworm	*Trichuris trichiura*	Overall STHs only	Total studies with references
Targeted delivery	20 studies, 23 papers	19 studies, 21 papers	20 studies, 22 papers	2 studies	25 studies, 28 papers
Mass delivery	18 studies, 22 papers	21 studies, 25 papers	18 studies, 22 papers	1 study	24 studies, 28 papers
Both targeted and mass delivery	7 studies, 8 papers	7 studies, 8 papers	7 studies, 8 papers	0 studies	7 studies, 8 papers

Full references for included studies are presented in the appendix. STH=soil-transmitted helminth.

Table 1: **Numbers of included studies according to method of drug delivery, stratified by type of STH**

do this we pooled PRatio, but reported results as 1−PRatio=PReduc. Results from each study were pooled using the inverse variance heterogeneity model,[33] which uses a quasi-likelihood-based variance structure without distributional assumptions and has been shown to perform better than the random effects method.[34] Heterogeneity was assessed using Cochran's Q test and Higgins' I^2, with I^2 greater than 50% considered to indicate significant heterogeneity. Publication bias and evidence of small-study effects were assessed using visual inspection of funnel plots,[35] and Egger's regression test (two-tailed p<0·1 considered indicative of asymmetry).[36]

Sensitivity analyses were done based on the following criteria: exclusion of influential studies (defined as studies with weight ≥30%); restriction to studies published in Africa; restriction to studies published in Asia; restriction to studies that used the Kato-Katz diagnostic method, recommended by WHO;[8] exclusion of studies that implemented WASH improvements; and prevalence reduction truncated as in the generalised linear model.

All meta-analyses, sensitivity analyses and the generalised linear model were re-run using random effects model weights for comparison. Meta-analyses were done with MetaXL (version 5.1). The generalised linear model was run in Stata (version 14.1).

Role of the funding source

There was no funding source for this study. The corresponding author (NEC) and senior author (SVN) had full access to all the data and had final responsibility for the decision to submit for publication.

Results

After title and abstract screening, 155 full-text articles were considered for inclusion, including 14 which were identified from manual searching of reference lists. 64 papers representing 56 individual studies met the inclusion criteria for the systematic review. 38 of these studies were suitable for meta-analysis (figure 1). Details of studies that were included and excluded are in the appendix (pp 3–7).

25 (45%) of 56 included studies reported on targeted drug administration and 24 (43%) studies reported on mass drug administration. Seven (13%) studies used both strategies (table 1). Most studies of targeted delivery used school-based deworming (23 [92%] of 25 studies) and treated only primary-school-aged children, generally aged 5–14 years (20 [80%] of 25; appendix p 8). Only four studies of school-based deworming included an attempt to include non-enrolled children.[37–40] In studies of mass delivery, the most common exclusion criteria for treatment were pregnancy (11 studies), and children younger than 2 years (11 studies) or 3 years (four studies; appendix p 8).

	Odds ratio (95% CI)	p value	R^2
Ascaris lumbricoides			
Mass *vs* targeted treatment	16·4 (2·1–125·8)	0·0092	0·724
Baseline prevalence*	2·7 (0·03–239·7)	0·6555	
Number of drug doses	1·8 (0·51–6·1)	0·3507	
Follow-up time	0·37 (0·27–0·51)	<0·0001	
Hookworm			
Mass *vs* targeted treatment	4·6 (1·8–11·6)	0·0020	0·336
Baseline prevalence*	0·07 (0·01–0·77)	0·0304	
Number of drug doses	0·82 (0·39–1·7)	0·5906	
Follow-up time	0·92 (0·81–1·0)	0·1797	
Trichuris trichiura			
Mass *vs* targeted treatment	2·1 (0·30–14·8)	0·4281	0·362
Baseline prevalence*	0·09 (0·004–2·0)	0·1228	
Number of drug doses	0·76 (0·35–1·6)	0·4568	
Follow-up time	0·55 (0·25–1·2)	0·1186	

STH=soil-transmitted helminth. *Baseline prevalence data were entered into the model on a scale of 0–1.

Table 2: **Odds ratio for selected covariates, stratified by STH (inverse variance weighted logit-linear regression with robust error variance)**

Of the seven studies that used both mass and targeted delivery, four studies alternated between the two strategies over time,[41–44] whereas three studies used different strategies in different regions, depending on the setting (rural *vs* urban),[45] *Schistosoma mansoni* prevalence,[40] or lymphatic filariasis prevalence.[46] There were no head-to-head comparisons of mass and targeted strategies in any study.

The number of anthelmintic drug doses varied from one to 16 doses, with dosing intervals ranging from 3 to 12 months, although interruptions in planned dosing schedules occasionally led to longer intervals.[41,45,47] The most common dosing intervals were 6 and 12 months, reported in 19 studies (6 months) and 20 studies (12 months). Drug administration strategies, as well as drug doses and study populations, are further described in the appendix (p 8).

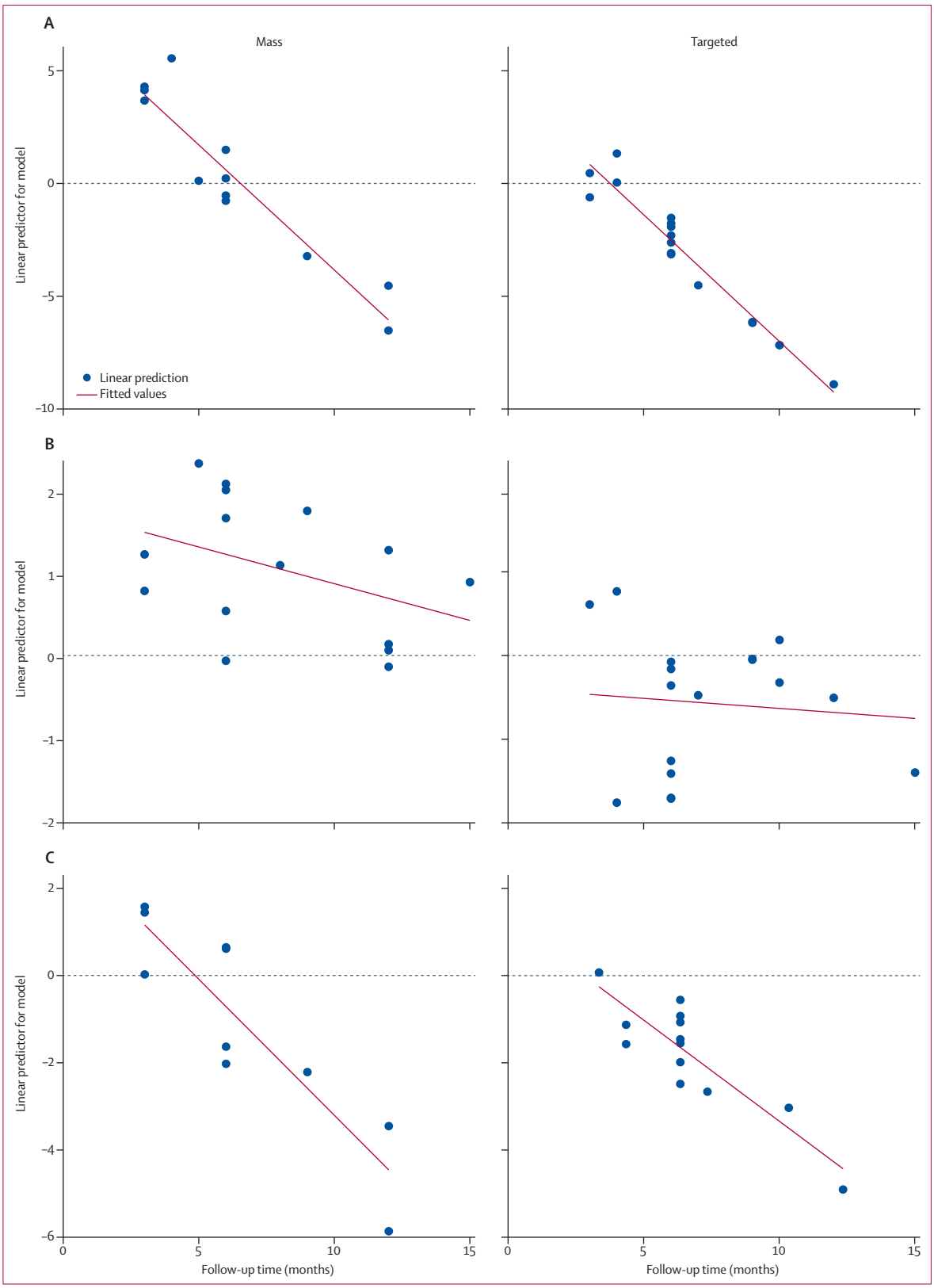

***Figure 2*: Contribution of follow-up time to the model**
(A) *Ascaris lumbricoides*. (B) Hookworm. (C) *Trichuris trichiura*. Relationship between the linear predictor from the model and follow-up time, stratified by method of delivery (mass *vs* targeted). The line depicts an overlaid linear fit to the plot data.

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Follow-up prevalence assessment ranged from 3 months to 3 years after the final drug dose; 6 months was the most common follow-up time (21 [38%] of 56 studies).

Most studies used the Kato-Katz method for diagnosis of soil-transmitted helminth infection (47 [84%] of 56 studies). Other methods included the formalin-ether sedimentation technique (five studies), direct smear technique (three studies), and the Harada-Mori technique (two studies). The formalin-detergent sedimentation technique,[48] single coproculture,[49] double coverslip method,[50] and real-time PCR for *A lumbricoides* only[51] were used in one study each. Two studies did not report the parasitological technique that was used.[38,52]

The most common additional medications were praziquantel (16 studies), diethylcarbamazine (nine studies), and ivermectin (five studies). Health education (eg, posters, leaflets, and information sessions) was reported in 14 studies. WASH improvements were described in eight studies, two of which had control groups that received drug treatment only. Additional interventions are summarised in the appendix (p 9).

34 studies (61%) reported treatment coverage for at least one round of drug administration. Two of these studies relied on self-reporting to measure coverage, whereas the remainder reported coverage recorded by the team responsible for drug administration. Coverage rates were highly variable, even within studies (at different rounds or in different regions), with the lowest reported coverage 29·3% and the highest 100%.

Nine potential deficiencies were assessed in terms of risk of bias (appendix pp 10–11). Of these deficiencies, the most common were response rate of less than 75% (or not reported) in 27 studies, deworming medications delivered to less than 75% of target population (or not reported) in 24 studies, use of different population sampling methods at baseline and follow-up (or not reported) in 11 studies, and non-representativeness of the general population (or target population not reported) in ten studies. All other deficiencies were less common and observed in a maximum of seven studies.

Results from the weighted regression model are shown in table 2. For *A lumbricoides*, 29 studies were included in the model. Mass drug distribution had a significantly greater effect on prevalence reduction than targeted drug distribution (OR 16·4, 95% CI 2·1–125·8; p=0·0092). Follow-up time was also strongly associated with prevalence reduction; for each 1 month increase, the odds of prevalence reduction decreased by 63% compared with baseline (0·37, 0·27–0·51; p<0·0001). Number of drug doses and baseline prevalence did not significantly contribute to prevalence reduction.

For hookworm, 32 studies were included in the model after exclusion of one study that was an outlier causing unstable estimates.[43] Mass drug distribution had a significantly greater effect on prevalence reduction than targeted distribution (OR 4·6, 95% CI 1·8–11·6; p=0·0020; table 2). Baseline prevalence was also associated with prevalence reduction (0·07, 0·01–0·77, p=0·0304). Follow-up time and number of drug doses did not have a significant effect on prevalence reduction.

Based on 23 studies included in the model, no significant effect was seen for mass versus targeted delivery, follow-up time, number of doses, or baseline prevalence for *T trichiura*.

Link specification tests showed that the models were correctly specified (squared linear predictor was not statistically significant; data not shown).[53] A scatter plot of the linear predictor against the true value of the outcome variable showed a reasonable fit through visual inspection of the data (data not shown).

The contribution of follow-up time to the variance explained by the linear model for each soil-transmitted helminth is shown in figure 2. The graphs are stratified by delivery strategy, depicting the differential effects of mass and targeted strategies as assessed by the model (the outcome variable PReduc is presented on the logit scale).

The results of the secondary analyses synthesising the non-truncated prevalence reduction estimates from individual studies are shown in table 3. Results are presented separately for studies of mass and targeted distribution, stratified by follow-up time. Heterogeneity among included studies was high. In targeted studies, I^2 was 97% for *A lumbricoides* and hookworm, and 96% for *T trichiura*. In mass studies, I^2 was 89% for *A lumbricoides*, 49% for hookworm, and 66% for *T trichiura*.

Sensitivity analyses to examine effect sizes when only studies from geographically similar locations were included, when only studies that used the Kato-Katz method were included, when influential studies were excluded, when studies that implemented WASH improvements were excluded, and when prevalence reduction was truncated as in the generalised linear model, showed that the results remain robust when these selection criteria are applied (appendix p 12).

The results of analyses using the random effects model weights are depicted in the appendix (pp 13–15). Re-analysis with this conventional approach did not substantially alter the results.

Egger's regression showed evidence of funnel plot asymmetry for *A lumbricoides* (intercept –3·68, p=0·0024), hookworm (intercept –4·34, p<0·0001), and *T trichiura* (intercept –2·578, p=0·0095). Funnel plots for each soil-transmitted helminth are shown in the appendix (p 16); to account for heterogeneity, plots were created separately according to delivery strategy and follow-up time. On visual inspection, minor asymmetry was noted for *T trichiura*, with more asymmetry for hookworm and *A lumbricoides*.

Discussion

Although studies examining the control of soil-transmitted helminth infections have been reported in

	Follow-up time	PReduc* (95% CI)	Cochran's Q	p value (Cochran's Q)	Number of study datasets
Ascaris lumbricoides					
Mass	6 months or less	0·52 (–0·10 to 0·79)	86·9	<0·0001	9
	More than 6 months	0·23 (0·02 to 0·40)	0·35	0·8390	3
Targeted	6 months or less	0·38 (0·12 to 0·57)	243·6	<0·0001	11
	More than 6 months	–0·01 (–0·45 to 0·30)	41·7	<0·0001	6
Hookworm					
Mass	6 months or less	0·72 (0·51 to 0·84)	14·1	0·0495	8
	More than 6 months	0·67 (0·47 to 0·79)	12·3	0·0546	7
Targeted	6 months or less	0·11 (–0·20 to 0·33)	336·4	<0·0001	10
	More than 6 months	0·30 (–0·21 to 0·59)	246·4	<0·0001	8
Trichuris trichiura					
Mass	6 months or less	0·14 (–0·22 to 0·40)	15·8	0·0148	7
	More than 6 months	0·23 (–0·49 to 0·60)	10·1	0·0066	3
Targeted	6 months or less	0·12 (–0·11 to 0·30)	294·9	<0·0001	9
	More than 6 months	0·13 (–0·08 to 0·30)	16·5	0·0003	3

Data are shown separately for mass and targeted studies for each STH and stratified by follow-up time. STH=soil-transmitted helminth. *PReduc=1–PRatio.

***Table 3*: Meta-analysis results synthesising non-truncated prevalence reduction estimates from individual studies**

the literature for over 90 years,[54] global interest in controlling these highly prevalent infections has surged in the past two decades. Resources committed to soil-transmitted helminth control have substantially increased; as such, identification of optimal drug delivery strategies is crucial to ensure effective use of these resources. To our knowledge, this systematic review and meta-analysis is the first synthesis of existing empirical evidence of the effect of mass and targeted drug distribution strategies on soil-transmitted helminth prevalence in school-aged children.

The results of this meta-analysis show that prevalence reduction of hookworm in school-aged children is significantly greater after mass deworming than after targeted deworming. This finding fits with existing knowledge that prevalence and intensity of hookworm infections peak in adulthood,[55] and that child-targeted programmes are thus unlikely to significantly reduce community transmission.[19] Because hookworm larvae have a short life expectancy in soil,[56] differential effects of targeted and mass deworming on environmental contamination and reinfection should become apparent soon after deworming. Our findings concur with results from mathematical modelling studies, which suggest that community-wide treatment would have a larger impact on environmental hookworm reservoirs, and therefore on reinfection, than would targeted treatment.[17,19,20]

Notably, results of this meta-analysis also show that mass deworming has a greater effect on prevalence reduction of *A lumbricoides* than does targeted deworming. Unlike hookworm, prevalence and intensity of *A lumbricoides* is highest in school-aged children,[2] and its infective stages can persist for several months in the environment.[56] Although findings from a modelling study[17] suggest that the current child-focused WHO guidelines will have a major impact on *A lumbricoides* levels by 2020, our results suggest that greater gains could be made if treatment was expanded to the community. The strong inverse association seen in our regression model between prevalence reduction and follow-up time for *A lumbricoides* agrees with a systematic review of soil-transmitted helminth reinfection following drug treatment,[7] which lends support to the validity of our findings.

No effect of mass versus targeted drug distribution on prevalence reduction was seen for *T trichiura*. Albendazole and mebendazole are known to have poor efficacy against *T trichiura*.[6,57] Therefore, it is unsurprising that community-wide treatment would not significantly enhance prevalence reduction, because environmental reservoirs of infective stages would remain high, and reinfection would occur rapidly after any successful treatment. This finding highlights the need for new drugs and drug combination strategies in areas with high *T trichiura* prevalence.[17,58]

There was significant heterogeneity in prevalence reduction among included studies, with wide CIs around odds ratios obtained in our regression models. This result is unsurprising, because studies were done in different countries, with variation in environmental conditions, WASH access, and economic contexts. Heterogeneity was particularly high in studies of targeted control programmes, suggesting that the effect of mass treatment programmes could be more consistent across different settings.

Egger's regression and funnel plots showed evidence of asymmetry, which probably reflects heterogeneity among studies. Small studies, which focus on a small number of schools or communities, might have led to greater prevalence reductions than large studies because of higher deworming coverage in smaller target populations. Publication bias is another possible reason, wherein studies showing little effect of deworming could be less likely to be published than studies showing significant impact. Such concerns have previously been raised in systematic reviews of the effect of deworming on morbidity indicators.[59]

This systematic review and meta-analysis adheres to PRISMA guidelines,[24] and a comprehensive search strategy was used. However, several limitations must be acknowledged. Heterogeneity among studies introduces the possibility of confounding by variables that were not included in our regression model. We were unable to control for factors such as environmental conditions, WASH access, and socioeconomic situation, all of which are known to influence the effect of deworming programmes.[60] Additionally, deworming coverage was not taken into account in our analyses. As we aimed to measure the differential effect of mass and targeted drug administration campaigns in real-life settings, we felt it inappropriate to exclude studies with low deworming

coverage, because coverage and compliance issues are important challenges facing these campaigns.[61]

We used soil-transmitted helminth prevalence to measure the effect of deworming programmes. High-intensity infections are known to cause most soil-transmitted-helminth-associated morbidity,[56] and some individuals harbour a disproportionately high worm burden.[62] Thus, prevalence might not accurately reflect associated morbidity in children in a community. However, preva-lence is the most widely-reported outcome measure in studies assessing deworming campaigns. Mean intensity of infection is not thought to be a reliable indicator of soil-transmitted-helminth-associated morbidity or an appropriate measure of the effect of soil-transmitted helminth control programmes.[63] Insufficient numbers of studies have reported on the prevalence of moderate-intensity and high-intensity infections for the analysis of pooled estimates.

The Kato-Katz diagnostic method, used by most studies in this analysis, is known to have reduced sensitivity in low-intensity settings.[64] This represents a potential source of measurement error that would bias results towards the null hypothesis, resulting in an underestimation of the differential effect of mass and targeted treatment.

Finally, we used standardised weights to calculate prevalence in school-aged children when age-stratified data were not available. These weights have been used in large-scale analyses including a global epidemiological disease burden study in 2010.[1] However, distribution of both age and soil-transmitted helminth prevalence might vary between communities, and prevalence reduction in school-aged children might differ from other age groups.

The results of this meta-analysis support the benefits of expanding drug treatment programmes to all community members. Given the potential for bias due to unmeasured confounders, these results also highlight the need for adequately powered cluster-randomised controlled trials examining the differential effect of mass and targeted treatment programmes. We are currently investigating the differential effect of school-based and community-based integrated soil-transmitted helminth control programmes in a pilot study in Timor-Leste.[65] A large cluster-randomised controlled trial assessing the effect of school-based versus community-based deworming on soil-transmitted helminth prevalence is also underway in Kenya.[66]

One concern is that the scaling up of mass drug administration programmes could exert additional drug pressure on soil-transmitted helminths, and potentially select for anthelmintic-resistant parasite genotypes.[5,67] Although no conclusive evidence exists for anthelmintic resistance of soil-transmitted helminths in human beings,[67] benzimidazole resistance is widespread in livestock.[68] Close monitoring of drug effectiveness during mass drug administration campaigns, as well as development of new anthelmintics, are important priorities for researchers, countries in which these campaigns are implemented, and their implementation partners.[2,67,68]

Integration of deworming programmes with WASH improvements should also be emphasised. By reducing environmental contamination with, and human exposure to, helminth infective stages, WASH interventions are a key component of sustainable soil-transmitted helminth control.[69–71] Such interventions are more expensive and complex than deworming campaigns, requiring infra-structure improvements and long-term behavioural change, and should be implemented alongside drug administration programmes designed to reduce soil-transmitted helminth prevalence and infection intensity.[72]

From a programmatic point of view, scaling up from targeted drug administration to mass drug administration has important economic implications for drug donation and soil-transmitted helminth control programmes. Current donations from pharmaceutical companies reach approximately 70% of at-risk children; expanding to mass treatment would require a substantial increase in the amount of drugs required. An increase in resources to support implementation—probably including additional international aid—would also be needed.[23] Although mass treatment campaigns for neglected tropical diseases such as onchocerciasis and lymphatic filariasis show the feasibility of providing community-wide treatment,[73,74] sustaining community-wide deworming long term might be difficult in some areas of sub-Saharan Africa and southeast Asia,[22] because of limited health system resources and capacity. However, in many transmission settings, mass deworming might eventually interrupt soil-transmitted helminth transmission such that drug treatment is no longer needed, whereas this could not be achieved in most settings with targeted deworming.[20,22,70]

Our analysis of existing empirical evidence agrees with mathematical modelling[20,22,23] and cost-effectiveness analyses,[21,23] highlighting the benefits of expanding soil-transmitted helminth control programmes to all age groups in endemic countries. Our findings lend support to calls to re-evaluate global soil-transmitted helminth control guidelines.[75] In view of the substantial global disease burden of soil-transmitted helminth infections and worldwide attention focused on the elimination of neglected tropical diseases, consideration of expansion to community-wide treatment needs to be prioritised.

Contributors

NEC did the database searches, data extraction, quality assessment, and statistical analysis, and drafted the manuscript. SAD and ACAC provided statistical guidance. SAD created and reviewed the statistical models. DW and SJC assisted with database searches, data extraction, and drafting of the manuscript. SVN conceived and designed the review protocol, and assisted with data extraction, quality assessment, and drafting the manuscript. ACAC and DG provided input into the review protocol. All authors edited and revised the manuscript.

Declaration of interests

We declare no competing interests.

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