The impact of ivermectin, diethylcarbamazine citrate, and albendazole mass drug administration on the prevalence of scabies and soil-transmitted helminths in school-aged children in three municipalities in Timor-Leste: a before–after assessment

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Summary

Background Integrated programmes that use combination mass drug administration (MDA) might improve control of multiple neglected tropical diseases simultaneously. We investigated the impact of Timor-Leste's national ivermectin, diethylcarbamazine citrate, and albendazole MDA, for lymphatic filariasis elimination and soil-transmitted helminth (STH) control, on scabies, impetigo, and STH infections.

Methods We did a before–after study in six primary schools across three municipalities in Timor-Leste (urban [Dili], semi-urban [Ermera], and rural [Manufahi]) before (April 23 to May 11, 2019) and 18 months after (Nov 9 to Nov 27, 2020) MDA delivery between May 17 and June 1, 2019. Study participants included schoolchildren, as well as infants, children, and adolescents who were incidentally present at school on study days. All schoolchildren whose parents provided consent were eligible to participate in the study. Infants, children, and adolescents younger than 19 years who were not enrolled in the school but were incidentally present at schools on study days were also eligible to participate if their parents consented. Ivermectin, diethylcarbamazine citrate, and albendazole MDA was implemented nationally, with single doses of oral ivermectin (200 µg/kg), diethylcarbamazine citrate (6 mg/kg), and albendazole (400 mg) administered by the Ministry of Health. Scabies and impetigo were assessed by clinical skin examinations, and STHs using quantitative PCR. The primary (cluster-level) analysis adjusted for clustering while the secondary (individual-level) analysis adjusted for sex, age, and clustering. The primary outcomes of the study were prevalence ratios for scabies, impetigo, and STHs (*Trichuris trichiura*, *Ascaris lumbricoides*, *Necator americanus*, and moderate-to-heavy *A lumbricoides* infections) between baseline and 18 months from the cluster-level analysis.

Findings At baseline, 1043 (87·7%) of 1190 children registered for the study underwent clinical assessment for scabies and impetigo. The mean age of those who completed skin examinations was 9·4 years (SD 2·4) and 514 (53·8%) of 956 were female (87 participants with missing sex data were excluded from this percentage calculation). Stool samples were received for 541 (45·5%) of 1190 children. The mean age of those for whom stool samples were received was 9·8 years (SD 2·2) and 300 (55·5%) were female. At baseline, 348 (33·4%) of 1043 participants had scabies, and 18 months after MDA, 133 (11·1%) of 1196 participants had scabies (prevalence ratio 0·38, 95% CI 0·18–0·88; p=0·020) in the cluster-level analysis. At baseline, 130 (12·5%) of 1043 participants had impetigo, compared with 27 (2·3%) of 1196 participants at follow-up (prevalence ratio 0·14, 95% CI 0·07–0·27; p<0·0001). There was a significant reduction in *T trichiura* prevalence from baseline (26 [4·8%] of 541 participants) to 18-month follow-up (four [0·6%] of 623 participants; prevalence ratio 0·16, 95% CI 0·04–0·66; p<0·0001). In the individual-level analysis, moderate-to-heavy *A lumbricoides* infections reduced from 54 (10·0%; 95% CI 0·7–19·6) of 541 participants to 28 (4·5%, 1·2–8·4) of 623 participants (relative reduction 53·6%; 95% CI 9·1–98·1; p=0·018).

Interpretation Ivermectin, diethylcarbamazine citrate, and albendazole MDA was associated with substantial reductions in prevalence of scabies, impetigo, and *T trichiura*, and of moderate-to-heavy intensity *A lumbricoides* infections. Combination MDA could be used to support integrated control programmes to target multiple NTDs.

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For the Tetum translation of the abstract see **Online** for appendix 1

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Research in context

Evidence before this study

We searched PubMed, without language restrictions, from database inception to Jan 17, 2023, with the terms "scabies" and/or "soil-transmitted helminths" and "ivermectin" and "mass drug administration" or "preventive chemotherapy". Our search identified eight studies that assessed the impact of ivermectin mass drug administration (MDA) on scabies. Five were cluster-randomised trials done in the Pacific that evaluated ivermectin delivered as two doses, a week apart. These studies were published in Fiji and the Solomon Islands across 2015, 2019, 2020, and 2022, and found that two-dose ivermectin MDA reduced scabies prevalence by up to 94% at 12 months, 89% at 24 months, and 75% at 36 months. A non-inferiority trial in Fiji published in 2021 showed single-dose ivermectin MDA reduced scabies prevalence by 82% after 12 months and was non-inferior to a two-dose regimen. A before–after study in Tanzania investigated the effect of three annual rounds of single-dose ivermectin MDA for lymphatic filariasis elimination, showing an 81% relative reduction in scabies prevalence 1 year after the first round, with prevalence slightly increasing after the following two rounds. Similarly, another before–after study in The Gambia that assessed the effect of three doses of ivermectin MDA for malaria vector control found a 19·5% relative difference between intervention and control villages 9 months after MDA, but with a notable rebound after 2 years. We identified three key studies that assessed the effect of MDA using albendazole and ivermectin combination therapy on soil-transmitted helminths. Two studies, published in Tanzania in 2009 and Liberia in 2021, reported a 76–85% *Trichuris trichiura* prevalence reduction, a 64–74% hookworm prevalence reduction, and no significant difference in *Ascaris lumbricoides* prevalence 8–12 months after MDA for lymphatic filariasis. A randomised trial in Tanzania and Laos published in 2021 found that albendazole and ivermectin led to a cure rate of 66% for *T trichiura*, greater than an albendazole monotherapy group (cure rate 13%) after 6 months. No significant differences in cure rates between treatment groups were observed for *A lumbricoides* and hookworm in this study.

Added value of this study

To our knowledge, this study is the first evaluation of the effectiveness of ivermectin, diethylcarbamazine citrate, and albendazole MDA on scabies and soil-transmitted helminths outside a trial context. We observed significant reductions in the prevalence of scabies, impetigo, and *T trichiura* in the primary analysis, and in the prevalence of moderate-to-heavy *A lumbricoides* infections in the secondary analysis after adjusting for confounders, measured 18 months after MDA.

Implications of all the available evidence

This study provides evidence that supports the adoption of combination MDA to improve the integrated control of multiple neglected tropical diseases, specifically using single doses of albendazole and ivermectin for scabies, impetigo, and soil-transmitted helminths. In settings where lymphatic filariasis is not a public health problem, additional funding and drug procurement mechanisms for ivermectin should be sought to ensure sustained neglected tropical disease control.

Introduction

Neglected tropical diseases (NTDs) are a diverse group of diseases that together affect over 1 billion people globally,[1] disproportionately in resource-poor communities and perpetuating a poverty–disease cycle. NTDs are among the most frequently occurring infectious diseases and include conditions such as soil-transmitted helminth (STH) infections, scabies, and lymphatic filariasis, which are estimated to cause illness in 895 million people, 175 million people, and 64 million people, respectively, per annum.[1] A core control strategy for several NTDs involves the periodic, large-scale administration of efficacious drugs to at-risk populations, known as mass drug administration (MDA).

Some agents used in MDA programmes are efficacious against multiple NTDs, either alone or in combination with others. Combination MDA, which involves the delivery of multiple different drugs, might be a cost-effective approach to integrate control and elimination strategies for multiple NTDs.[2] However, there is a paucity of research investigating the effect of combination MDA.

WHO endorsed the addition of single-dose ivermectin to the double-drug MDA regimen (diethylcarbamazine citrate and albendazole) to improve control of lymphatic filariasis in settings in which double-drug MDA has not reached elimination targets,[3] after establishing safety in both adults and children, with the exception of pregnant women and children younger than 5 years in the case of ivermectin.[4] Triple-drug ivermectin, diethylcarbamazine citrate, and albendazole MDA might also improve control of STHs and scabies. MDA using two doses of oral ivermectin for scabies control is increasingly being used with promising results in the Pacific region,[5–7] and might be effective with a single dose.[8] For STHs, the WHO-recommended drugs albendazole or mebendazole[9] have poor efficacy against two major species, *Trichuris trichiura*[10] and *Strongyloides stercoralis*.[11] However, combining albendazole with ivermectin improves efficacy against *T trichiura*[10] and ivermectin monotherapy is highly efficacious against *S stercoralis*.[11]

Located in southeast Asia, Timor-Leste is a country divided into 13 municipalities, with an estimated total population of 1·3 million. Chronic malnutrition and infectious diseases (including tuberculosis, pneumonia, dengue, and NTDs) are major child health problems that affect the country.[12–14] In 2005, the Timor-Leste Ministry of Health initiated a national lymphatic filariasis and STH control programme, with support from WHO.[15] The programme was interrupted in 2008 because of

funding shortages and civil unrest, then resumed in 2015, with the plan to deliver five annual rounds of diethylcarbamazine citrate and albendazole MDA, complemented with additional annual school-based albendazole distribution in Dili municipality for STH control. This latter programme only took place in 2017 and 2018 (Timor-Leste Ministry of Health, personal communication). In 2019, ivermectin was added to the national MDA programme to accelerate the elimination of lymphatic filariasis as a public health problem.

In this study, we present the first assessment, to our knowledge, of the impact of this ivermectin, diethylcarbamazine citrate, and albendazole MDA on scabies, impetigo, and STH infections, to better understand the role of integrated MDA in controlling multiple NTDs in co-endemic countries.

Methods

Study design and participants

We used a before–after design to assess the impact of Timor-Leste's ivermectin, diethylcarbamazine citrate, and albendazole MDA for lymphatic filariasis and STH control (implemented between May 17 and June 1, 2019) on scabies, impetigo, and STHs. Cross-sectional surveys were done just before MDA (baseline; April 23 to May 11, 2019) and 18 months after MDA (follow-up; Nov 9 to Nov 27, 2020) in six primary schools across three municipalities (Dili, Ermera, and Manufahi; appendix 2 p 7). In Dili, an additional STH follow-up was completed 6 months after MDA (Nov 1 to Nov 6, 2019). Follow-up at all sites was planned for 12 months after MDA but was delayed because of COVID-19 restrictions.

The three municipalities were selected because they captured socioeconomic and geographical diversity including urban (Dili), semi-urban (Ermera), and rural (Manufahi) districts and for feasibility reasons, including previous research collaborations.[15,16] In Manufahi, two schools were selected from a list of schools that had been included in a previous study.[17] In Ermera and Dili, schools were selected from a list obtained through the Ministry of Education, with a preference for the largest primary schools that were easily accessible for fieldwork.

All schoolchildren whose parents provided consent were eligible to participate in the study. Infants, children, and adolescents younger than 19 years who were not enrolled in the school but were incidentally present at schools on study days were also eligible to participate if parents consented. Sex data (male or female) were self-reported by participants. Verbal consent was obtained from parents for participation in the skin examinations, as per previous local scabies research and preference of school principals and clinical staff, and approved by ethical review boards. Written consent was obtained for stool collection. The study was approved by the Instituto Nacional de Saúde in Timor-Leste (1545MS-INS/DE/X/2019) and University of New South Wales Ethics Board in Australia (HC190140).

Procedures

Ivermectin, diethylcarbamazine citrate, and albendazole MDA was implemented nationally between April 23 and May 11, 2019, with single doses of oral ivermectin (200 µg/kg), diethylcarbamazine citrate (6 mg/kg), and albendazole (400 mg) administered by the Ministry of Health, with 76% coverage (Timor-Leste Ministry of Health, personal communication). A school-based albendazole programme in Dili municipality only, planned for November, 2019, did not take place.

The research team undertook two preparatory visits to the six participating schools before data collection, the first to request approval from the school principal, and the second to ask teachers to inform parents to attend schools on an agreed date. Data collection occurred over a 3-day period in each school. On day one, the local project manager explained the study to parents and sought parental verbal consent for skin examinations and written consent for stool collection. Children for whom consent was obtained were then enrolled in the study and age and sex information was collected. Students were taught how to provide a stool sample, given stool collection kits containing a plastic specimen collection container, gloves, a plastic spoon, and a study information sheet, and asked to return a stool sample the following day. A team of clinicians did clinical skin examinations on day one. On days two and three, stool samples were collected and processed, and any outstanding skin examinations were completed.

See Online for appendix 2

A team of four local clinicians underwent a one-day training programme in the diagnosis of scabies, impetigo, and other common skin conditions, immediately before the study. All four passed a picture-based assessment with the minimum required competency of 80%. Examination of exposed skin, including arms, face, legs, and abdomen, was done for scabies and impetigo lesions in a well-lit classroom or outdoors. Scabies was diagnosed using the 2020 criteria published by the International Alliance for the Control of Scabies[18] in the categories of clinical scabies and suspected scabies. The severity of scabies was classified as very mild (1–2 lesions), mild (3–10 lesions), moderate (11–50 lesions) or severe (>50 lesions). Severity of impetigo was classified as very mild (1–5 lesions), mild (6–10 lesions), moderate (11–50 lesions) or severe (>50 lesions). At baseline, participants were advised of the planned Ministry of Health MDA, through which all participants aged 5 years and older would be offered ivermectin, diethylcarbamazine citrate, and albendazole. Children younger than 5 years would not be eligible for ivermectin, and therefore any children in this age group found to have scabies or impetigo were referred to local health clinics. At follow-up, all children were asked if they recalled participating in the 2019 ivermectin, diethylcarbamazine citrate, and albendazole MDA, and all children with scabies were provided with topical permethrin and instructions on how to apply it.

One 3-g sample of stool per participant was fixed in 3 mL of 5% (weight by volume) potassium dichromate upon receipt to preserve stool specimens and prevent bacterial and fungal growth and placed on ice to arrest egg development. Upon completion of fieldwork, samples were kept refrigerated and then couriered with ice packs to the University of Melbourne (Melbourne, VIC, Australia), where they were stored at 4°C until DNA extraction. Samples were in transit for 4 days. TaqMan probe-based multiplex quantitative (q)PCR was used to diagnose STH infections with six species (*Necator americanus, Ancylostoma ceylanicum, Ancylostoma duodenale, T trichiura, Strongyloides* spp, and *Ascaris lumbricoides*) and quantify intensity of infection with *N americanus*, *T trichiura*, and *A lumbricoides* through conversion of qPCR cycle threshold values into eggs per g of stool using previously derived equations, as follows:[19–22] *A lumbricoides* epg=$10^{([Ct-36{\cdot}970]/-3{\cdot}489)}$; *T trichiura* epg=$10^{([Ct-36{\cdot}730]/-3{\cdot}288)}$; *N americanus* epg=$10^{([Ct-35{\cdot}020]/-3{\cdot}641)}$, where Ct is the cycle threshold value and epg is eggs per g of stool. A separate set of equations were used for 6-month samples which were found to be embryonated through microscopic examination of a random subset of samples, as follows:[23] *A lumbricoides* epg=$10^{([Ct-30{\cdot}048]/-3{\cdot}2804)}$; *T trichiura* epg=$10^{([Ct-31{\cdot}888]/-4{\cdot}048)}$; *N americanus* epg=$10^{([Ct-32{\cdot}657]/-3{\cdot}878)}$. All qPCR assays were done in duplicate for each individual sample using TaqMan hydrolysis probes (Integrated DNA Technologies; Coralville, IA, USA) in a Mic qPCR cycler system (Bio Molecular Systems; Dural, NSW, Australia), where all samples were deemed positive when both replicates showed cycle threshold values. Further details on the qPCR methodology used, including the sequence of probes and primers, are summarised in appendix 2 (pp 1–2). The eggs per g of stool values estimated from the conversion formulae were classified into one of three infection intensity classes (light, moderate, heavy) according to WHO thresholds.[24]

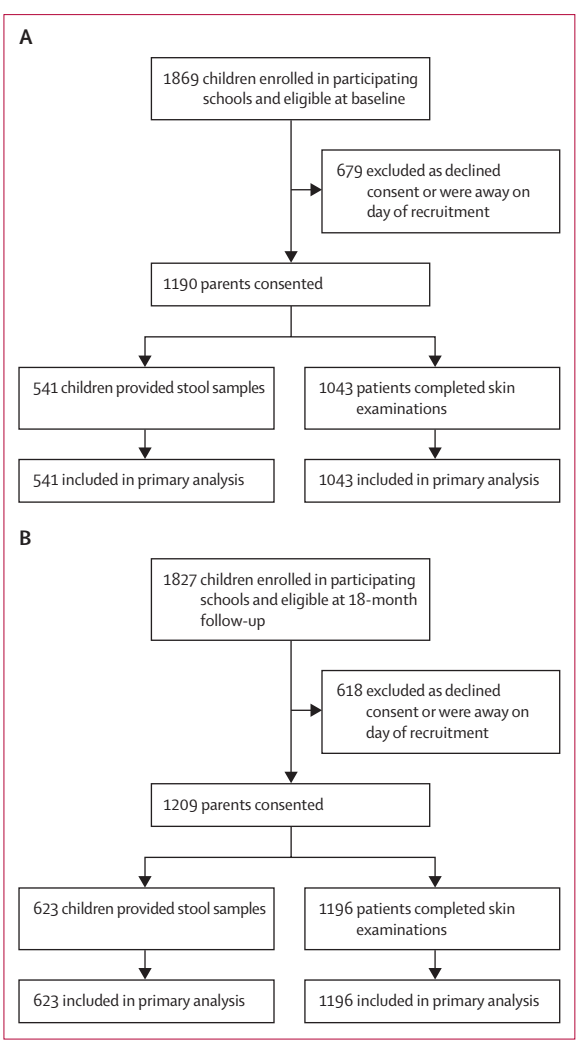

Figure: **Recruitment flowchart at baseline (A) and at 18-month follow-up (B)**

Outcomes

The primary outcomes were the prevalence ratios for scabies, impetigo, and STH (*T trichiura*, *A lumbricoides*, *N americanus*, and moderate-to-heavy *A lumbricoides* infections) between baseline and 18 months from a cluster-level analysis. Secondary outcomes were the relative prevalence reduction in scabies, impetigo, and STH infections, and the relative reduction in STH egg count, from an individual-level analysis.

Statistical analysis

We used a two-tailed, one sample binomial test for proportion to determine the required sample size to detect a predetermined minimum effect of MDA at 12 months, with 80% power and a 5% margin of error. For scabies, we assumed a baseline prevalence of 32% in Ermera and Manufahi, and 5·2% in Dili.[16] We conservatively assumed an MDA effect of 6% absolute difference in scabies prevalence in Ermera and Manufahi, and a 2% difference in Dili, giving a target sample size of 1730. Because of the low expected prevalence of *T trichiura*, STH sample size calculations were completed for *A lumbricoides* and hookworm.[15,17,25] We assumed baseline prevalence to be 11·8–23·4% for *A lumbricoides* and 2·4–4·8% for hookworm, depending on the municipality, based on 2012–16 survey data.[15,17,25] We conservatively predicted an absolute prevalence difference of 8·4–10·3% for *A lumbricoides* and 4·9–6·2% for hookworm infections based on a published predictive model.[26] Assuming a 20% non-response rate, a sample size of 900 per survey was required. However, we did not reach the target sample size and, therefore, recalculated the power for each outcome of interest with the achieved sample sizes. When incorporating the number of clusters, mean cluster size, and observed intra-cluster correlation coefficients for each disease outcome, the study had more than 80% power to detect observed differences in the prevalence of scabies, impetigo, and *T trichiura*. There was inadequate power

(<20%) to detect a difference in *N americanus* and *A lumbricoides* prevalence if the observed changes reflected a true difference. We also had sufficient power (84%) to assess the 6-month impact of MDA on *A lumbricoides* in Dili.

We evaluated the overall intervention impact at both the cluster (school) and individual (students) level while adjusting for confounding. In the primary analysis, the intervention impact was assessed using a cluster-level analysis based on school-level estimates and between-school variability, rather than at the individual level. After calculating disease prevalence in each of the six clusters (schools) separately at baseline and follow-up, we calculated the prevalence ratios for each cluster (ie, school), defined as prevalence before MDA divided by prevalence after MDA in each cluster. We calculated the overall pooled prevalence ratios and estimated 95% CIs using a paired *t* test based on the pooled SD. We report unadjusted prevalence estimates and cluster-adjusted prevalence ratios.

In the secondary analysis, we assessed the intervention impact using generalised linear models with individual-level observations (students) adjusted for school-level clustering using robust clustered SEs, and for age group and sex using fixed-effect terms. We report adjusted prevalence estimates, absolute prevalence differences, relative prevalence differences, and incidence rate ratios (RRs; mean egg count at follow-up divided by mean egg count at baseline). We also used an individual-level generalised linear model to assess the 6-month impact of MDA on *A lumbricoides* in Dili. p<0·05 was considered to indicate a significant difference.

Analyses were done in Stata version 14.2.

Role of the funding source

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

Results

At baseline, 1043 (87·7%) of 1190 children registered for the study underwent clinical assessment for scabies and impetigo (figure; appendix 2 pp 2–3). The mean age of those who completed skin examinations was 9·4 years (SD 2·4) and 514 (53·8%) of 956 were female (87 patients with missing sex data were excluded from this percentage calculation). Stool samples were received for 541 (45·5%) of 1190 children. The mean age of those for whom stool samples were received was 9·8 years (SD 2·2) and 300 (55·5%) were female (table 1).

At 18-month follow-up, 1196 (98·9%) of 1209 children who registered for the study completed clinical skin assessment and 623 (51·5%) of 1209 children provided a stool sample (figure; appendix 2 pp 2–3). Sex and age characteristics were similar to baseline (table 1). Overall, 1066 (88·2%) of 1209 children reported having received ivermectin, diethylcarbamazine citrate, and albendazole. Demographic characteristics and self-reported ivermectin, diethylcarbamazine citrate, and albendazole uptake were similar between children who provided a stool sample and those who did not (appendix 2 p 4).

	Baseline		18 months	
	Stool samples (n=541)	Skin examinations (n=1043)	Stool samples (n=623)	Skin examinations (n=1196)
Municipality				
Dili	203 (37·5%)	497 (47·7%)	315 (50·6%)	611 (51·1%)
Ermera	201 (37·2%)	363 (34·8%)	262 (42·1%)	412 (34·5%)
Manufahi	137 (25·3%)	183 (17·6%)	46 (7·4%)	173 (14·5%)
Sex				
Male	241 (44·5%)	442/956 (46·2%)*	287 (46·1%)	592 (49·5%)
Female	300 (55·5%)	514/956 (53·8%)*	336 (53·9%)	604 (50·5%)
Age, years				
0–4	1 (0·2%)	25/965 (2·6%)*	0	1 (0·1%)
5–9	233 (43·1%)	445/965 (46·1%)*	241 (38·7%)	506 (42·3%)
10–14	299 (55·3%)	487/965 (50·5%)*	375 (60·2%)	671 (56·1%)
≥15	8 (1·5%)	8/965 (0·8%)*	7 (1·1%)	18 (1·5%)
Mean (SD)	9·8 (2·2)	9·4 (2·4)*	10·1 (2·1)	10·0 (2·2)

Data are n (%) or n/N (%), unless otherwise indicated. *Participants with missing sex (n=87) and age (n=78) data were excluded from calculations.

Table 1: **Demographics of participants who provided stool samples and underwent clinical skin examinations at baseline and 18-month follow-up**

At baseline, 348 (33·4%) of 1043 participants had scabies, and 18 months after MDA, 133 (11·1%) of 1196 participants had scabies (table 2; prevalence ratio 0·38, 95% CI 0·18–0·88; p=0·020) in the cluster-level analysis. Similarly, at baseline 130 (12·5%) of 1043 participants had impetigo, compared with 27 (2·3%) of 1196 participants at follow-up (prevalence ratio 0·14, 95% CI 0·07–0·27; p<0·0001). At baseline, 104 (10·0%) of 1043 participants had moderate-to-severe scabies, compared with 79 (6.6%) of 1196 participants at 18-month follow-up; this difference was not significant. In the individual-level analysis, although the broad pattern of results was similar to the cluster-level analysis, there was also a significant relative reduction in the prevalence of moderate-to-severe intensity scabies infections after controlling for age and sex (appendix 2 p 5).

There was a significant reduction in *T trichiura* prevalence from baseline (26 [4·8%] of 541 participants) to 18-month follow-up (four [0·6%] of 623 participants; table 2; prevalence ratio 0·16, 95% CI 0·04–0·66; p<0·0001). We did not detect a statistically significant difference in the prevalence of *A lumbricoides* or *N americanus* infections (table 2). Baseline prevalence of *A ceylanicum*, *A duodenale*, and *Strongyloides* spp was less than 2% (six or less infected participants).

We did not detect a significant difference in mean egg count for infections with *T trichiura* (incidence RR 1·68, 95% CI 0·41–6·80; p=0·47), *A lumbricoides* (1·12, 0·44–2·86; p=0·82), or *N americanus* (0·89, 0·48–1·65;

	Baseline (six clusters)		18 months (six clusters)		Cluster-adjusted prevalence ratio (95% CI); p value
	n/N	Prevalence (95% CI)	n/N	Prevalence (95% CI)	
Scabies	348/1043	33·4% (30·6–36·3)	133/1196	11·1% (9·5–13·0)	0·38 (0·18–0·88); p=0·020
Moderate-to-severe scabies infections (prevalence)	104/1043	10·0% (8·3–12·0)	79/1196	6·6% (5·3–8·2)	0·74 (0·27–2·08); p=0·58
Moderate-to-severe scabies infections (proportion)	104/348	30·0% (25·3–34·9)	79/133	59·4% (50·8–67·5)	1·99 (1·6 –2·47); p=0·045
Impetigo	130/1043	12·5% (10·6–14·6)	27/1196	2·3% (1·6–3·3)	0·14 (0·07–0·27); p<0·0001
T trichiura	26/541	4·8% (3·3–7·0)	4/623	0·6% (0·2–1·7)	0·16 (0·04–0·66); p<0·0001
T trichiura moderate-to-heavy intensity infections	1/541	0·2% (0·3–1·3)	0	0	NA
A lumbricoides	98/541	18·1% (15·1–21·6)	82/623	13·2% (10·7 –16·1)	0·85 (0·34–2·07); p=0·74
A lumbricoides moderate-to-heavy intensity infections	54/541	10·0% (7·7–12·8)	28/623	4·5% (3·1–6·4)	0·45 (0·11–1·83); p=0·23
N americanus	40/541	7·4% (5·5–9·9)	37/623	5·9% (4·3 – 8·1)	0·58 (0·13–2·56); p=0·46
N americanus moderate-to-heavy intensity infections	1/541	0·2% (0·3–1·3)	4/623	0·6% (0·2–1·7)	NA
A ceylanicum	3/541	0·6% (0·2–1·7)	21/623	3·4% (2·2–5·1)	NA
A duodenale	1/541	0·2% (0·3–1·3)	0	0	NA
Strongyloides spp	6/541	1·1% (0·5–2·5)	5/623	0·8% (0·3–1·9)	NA

Infection intensity not summarised for *A duodenale*, *A ceylanicum*, and *Strongyloides* spp as we were unable to obtain the eggs needed for egg count calculations. *A ceylanicum*=*Ancylostoma ceylanicum*. *A duodenale*=*Ancylostoma duodenale*. *A lumbricoides*=*Ascaris lumbricoides*. NA=not applicable due to insufficient power for analysis. *N americanus*=*Necator americanus*. *T trichiura*=*Trichuris trichiura*.

Table 2: **Cluster-adjusted prevalence ratios of scabies, impetigo, and soil-transmitted helminths between baseline and 18 months after mass drug administration (cluster-level analysis)**

	Baseline		18 months		Incidence rate ratio (95% CI); p value
	Infected, n	Mean eggs per g of stool (SD)	Infected, n	Mean eggs per g of stool (SD)	
Trichuris trichiura	26	130 (296)	4	77·7 (94·0)	1·68 (0·41–6·80); p=0·47
Ascaris lumbricoides	98	20 083 (35 288)	82	17 975 (40 195)	1·12 (0·44–2·86); p=0·82
Necator americanus	40	456 (817)	37	514 (1011)	0·89 (0·48–1·65); p=0·71

Infection intensity was not summarised for *Ancylostoma duodenale*, *Ancylostoma ceylanicum*, and *Strongyloides* spp as we were unable to obtain the eggs needed for egg count calculations.

Table 3: **Cluster-adjusted soil-transmitted helminth egg count at baseline and 18 months after mass drug administration (individual-level analysis)**

p=0·71; table 3). Similarly, we found no significant difference in the prevalence of moderate-to-heavy *A lumbricoides* infections (prevalence ratio 0·45, 95% CI 0·11–1·83; p=0·23; table 2).

In the individual-level analysis, the broad pattern of results remained similar except that we found a significant relative reduction in the prevalence of moderate-to-heavy intensity *A lumbricoides* infections after controlling for age and sex (a reduction from 54 [10·0%; 95% CI 0·7–19·6] of 541 participants to 28 [4·5%, 1·2–8·4] of 623 participants; relative reduction 53·6%; 95% CI 9·1–98·1; p=0·018; appendix 2 p 5).

In the Dili-specific analyses, there was an initial significant reduction in *A lumbricoides* infection prevalence between baseline (28 [13·8%] of 203 children) and 6 months (eight [4·6%] of 164 children; relative reduction 64·6%, 95% CI 59·0–70·2; p<0·0001) followed by a rebound to a similar prevalence to baseline at 18 months (table 4; 46 [14·6%] of 315 children; relative increase 199·4%, 95% CI 20·5–378·3; p=0·029). We found no significant reduction in *A lumbricoides* infection intensity from baseline to 6 months (incidence RR 1·61, 95% CI 0·39–6·61; p=0·51), with intensity at 18 months also similar to baseline (table 5; incidence RR 0·97, 95% CI 0·42–0·87; p=0·96).

Discussion

To our knowledge, this study is the first assessment of the impact of a national ivermectin, diethylcarbamazine citrate, and albendazole MDA programme for lymphatic filariasis and STH on scabies, impetigo, and STH infections. We observed substantial reductions in scabies, impetigo, and *T trichiura* prevalence in a cluster-level analysis, and in the prevalence of moderate-to-heavy *A lumbricoides* infections in an individual-level analysis after adjusting for confounders, 18 months after MDA.

The effectiveness of ivermectin MDA for scabies has previously been evaluated in community trials using two doses administered 7–14 days apart,[5–7] in line with therapeutic guidelines. However, a second dose increases implementation costs, representing a barrier for resource-constrained settings, and presents challenges for integration with other NTD programmes that use single-dose regimens. Our study is among the first to evaluate the effectiveness of single-dose ivermectin outside a trial context,[27] and our findings suggest that it might be an effective and practical strategy for longer-term control of scabies and impetigo. Our estimated scabies relative prevalence reduction after 18 months is broadly consistent with the results of a previous trial, which reported an 82% reduction after 12 months in its single-dose arm,[8] and the 81% reduction

	Baseline		6 months		18 months		Relative difference from baseline to 6 months (95% CI); p value	Relative difference from 6 months to 18 months (95% CI); p value	Relative difference from baseline to 18 months (95% CI); p value
	n/N	Prevalence (95% CI)	n/N	Prevalence (95% CI)	n/N	Prevalence (95% CI); p value			
A lumbricoides	28/203	13·8% (4·6 to 23·0)	8/164	4·9% (0·9 to 8·9)	46/315	14·6% (6·2 to 35·4)	−64·6% (59·0 to 70·2); p<0·0001	199·4% (20·5 to 378·3); p=0·029	5·9% (−74·2 to 85·9) p=0·89
A lumbricoides moderate-to-heavy intensity infections	15/203	7·4% (3·8 to 11·0)	5/164	3·0% (1·3 to 7·2)	18/315	5·7% (3·6 to 8·9)	NA	NA	NA
T trichiura	10/203	4·9% (2·7 to 9·0)	4/164	2·4% (0·9 to 6·4)	3/315	1·0% (0·3 to 3·0)	NA	NA	NA
T trichiura moderate-to-heavy intensity infections	1/203	0·5% (0·03 to 1·5)	0/164	0	2/315	0·6% (0·2 to 2·5)	NA	NA	NA
N americanus	15/203	7·4% (4·5 to 11·9)	5/164	3·0% (1·3 to 7·2)	22/315	7·0% (4·6 to 10·4)	NA	NA	NA
N americanus moderate-to-heavy intensity infections	1/203	0·5% (0·03 to 1·5)	0/164	0	0/315	0	NA	NA	NA
A duodenale	0/203	0	1/164	0·6% (0·1 to 4·3)	0/315	0	NA	NA	NA
A ceylanicum	1/203	0·5% (0·07 to 3·5)	0/164	0	5/315	1·6% (0·7 to 3·8)	NA	NA	NA
Strongyloides spp	3/203	1·5% (0·5 to 4·5)	0/164	0	1/315	0·3% (0·04 to 2·2)	NA	NA	NA

Infection intensity was not summarised for *A duodenale*, *A ceylanicum*, and *Strongyloides* spp as we were unable to obtain the eggs needed for egg count calculations. *A ceylanicum*=*Ancylostoma ceylanicum*. *A duodenale*=*Ancylostoma duodenale*. *A lumbricoides*=*Ascaris lumbricoides*. NA=not applicable due to insufficient power for analysis. *N americanus*=*Necator americanus*. *T trichiura*=*Trichuris trichiura*.

Table 4: **Soil-transmitted helminth prevalence at baseline, 6 months, and 18 months in Dili (individual-level analysis)**

	Baseline		6 months		18 months		Incidence rate ratio from baseline to 6 months (95% CI); p value	Incidence rate ratio from 6 months to 18 months (95% CI); p value	Incidence rate ratio from baseline to 18 months (95% CI); p value
	Infected, n	Mean eggs per g of stool (SD)	Infected, n	Mean eggs per g of stool (SD)	Infected, n	Mean eggs per g of stool (SD)			
Trichuris trichiura	10	286 (445)	4	2 (1)	3	102 (98)	NA	NA	NA
Ascaris lumbricoides	28	27 124 (39 472)	8	16 829 (26 204)	46	27 958 (51 220)	1·61 (0·39–6·61); p=0·51	0·60 (0·42–0·87); p=0·0067	0·97 (0·42–0·87); p=0·96
Necator americanus	15	759 (1117)	5	32 (43)	22	495 (889)	NA	NA	NA

Infection intensity was not summarised for *Ancylostoma duodenale*, *Ancylostoma ceylanicum*, and *Strongyloides* spp as we were unable to obtain the eggs needed for egg count calculations. NA=not applicable due to insufficient power for analysis.

Table 5: **Soil-transmitted egg count across baseline, 6-month follow-up, and 18-month follow-up in Dili (individual-level analysis)**

in an impact assessment of ivermectin MDA in Tanzania.[27] Potential reasons for the lower effect size in our study include the fact that no permethrin was administered to those who were ineligible for ivermectin; lower coverage in the programmatic setting and additional difficulties in delivering MDA nationally to a highly mobile population versus small island populations; the longer follow-up period; and a higher baseline burden. In the Tanzania study, the prevalence of scabies increased after a second MDA round, although it remained lower than at baseline.[27] Similarly, another before–after study in The Gambia that assessed the impact of three doses of ivermectin MDA for malaria vector control found a 19·5% relative difference between intervention and control villages 9 months after MDA but with a notable rebound after 2 years,[28] suggesting that repeated MDA is required to sustain control, regardless of the number of doses administered. We also observed a marked reduction in impetigo as has been seen in other studies.[6,7] This finding might be due to the reduction in scabies, given that impetigo is a common complication.

Albendazole and mebendazole have excellent therapeutic efficacy against *A lumbricoides* and moderate efficacy against hookworm, but little efficacy against *T trichiura*.[10] Albendazole MDA has poor programmatic effectiveness against *T trichiura*[29] but combination therapy with ivermectin has high therapeutic efficacy[10] and programmatic effectiveness.[30,31] Our observed prevalence reduction in *T trichiura* infections after 18 months is similar to findings from other studies that reported up to a 76% reduction after 12 months in the context of lymphatic filariasis elimination programmes[30,31]

and clinical trials,[32] suggesting that combination therapy can sustain impact, at least in lower-burden settings.

Programmatic delivery of albendazole and ivermectin in lymphatic filariasis and onchocerciasis elimination programmes has been shown to be effective at reducing *A lumbricoides* and hookworm prevalence and infection intensity for up to 12 months.[30,31] Although we did not detect an impact on the prevalence of *A lumbricoides* and hookworm, we observed a reduction in the prevalence of moderate-to-heavy intensity *A lumbricoides* infections in our individual-level analysis. Furthermore, in Dili, *A lumbricoides* prevalence decreased at six months, then returned to baseline prevalence at 18 months. This finding was unsurprising given that ongoing environmental contamination and transmission leads to reinfection, resulting in a rebound of prevalence to pre-treatment frequencies in the absence of additional MDA.[33]

Since the London Declaration on Neglected Tropical Diseases was signed in 2012, there has been a considerable scale-up of MDA programmes in endemic countries, largely relying on drug donation programmes. These drugs are generally earmarked for specific risk populations and diseases. Examples include The Mectizan Donation Program, which has donated over 4 billion ivermectin tablets for lymphatic filariasis and onchocerciasis control since 1987[34] and programmes by other biopharmaceutical companies that have donated over 2 billion doses of albendazole and mebendazole for STH control in school-aged children. Although some countries have been able to procure additional drugs to cover other groups, for example preschool aged children for STH control, there are inadequate drug supply and funding mechanisms to procure ivermectin and albendazole for MDA against STHs and scabies, to potentially achieve STH transmission interruption,[26] and control of scabies and impetigo. Our findings could be used to justify additional drug donations and provide empirical support for internal country funding mechanisms to enable integrated control of these diseases by use of combination MDA, even after lymphatic filariasis and onchocerciasis elimination targets are reached.

In Timor-Leste, lymphatic filariasis elimination targets have been met and therefore ivermectin, diethylcarbamazine citrate, and albendazole treatment was ceased after the 2019 MDA programme. Although initially planned, there has been no further school-based albendazole distribution for STH control in Dili. Given that STH infections and scabies remain substantial public health problems, further rounds of combination MDA using a single dose of ivermectin and albendazole to target STHs and scabies might be justified, and funding mechanisms or drug donations investigated if this is prioritised by the Timor-Leste Ministry of Health.

There are several limitations of this study. First, we assumed that observed reductions in disease burden were attributable to MDA; however, given the observational design of our study, we cannot rule out the effect of other non-pharmaceutical confounders or environmental factors during the study period. For instance, during the COVID-19 pandemic, travel restrictions were imposed, and physical distancing and frequent handwashing were promoted, which could have collectively affected scabies, impetigo, and STH transmission. In line with this limitation, future observational studies could benefit from measuring potentially confounding variables at baseline and follow-up, such as sociodemographic and water, sanitation, and hygiene factors, to be controlled for in statistical analyses. Second, although MDA was delivered to all eligible community members, our study population was restricted to children attending schools. Third, the present study surveyed only three of the 13 municipalities in Timor-Leste. Community-wide surveys done in additional municipalities would allow us to quantify the impact of MDA in all age groups, providing insight into the national impact of MDA. Finally, the non-random sampling method used might have restricted the generalisability of our findings. Conversely, our sampling method ensured that we could survey communities that are known to have a high scabies and STH burden.

In conclusion, our findings highlight the benefits of combination MDA, providing support for the integration of NTD programmes to accelerate attainment of multiple control targets concurrently, specifically using ivermectin and albendazole for scabies, impetigo, and STHs. In settings where lymphatic filariasis is not a public health problem, additional funding and drug procurement mechanisms will need to be sought to ensure sustained NTD control.

Contributors

All authors contributed substantially to the design of the study. NEC and BL were coprimary coordinators of fieldwork procedures and data collection. BL had primary responsibility for data curation, data analysis, and writing up the manuscript, and is primary author of the manuscript. SVN, JRF, and JK acquired funding for the study. SVN, JRF, NEC, RT, JK, AS, and DE designed the study methods. BL, SVN, and HW co-designed the statistical analysis strategy and verified the underlying data. BL did the statistical analysis with support from HW and SVN. SVN and JRF provided oversight and supervision of the study. BL, NEC, MAAM, SA, AM, SFH, PA, JY, NF, and JLF provided oversight and training for fieldwork procedures and coordinated data collection. SA was the primary in-field project manager in Timor-Leste. SFH completed the quantitative PCR analysis with support from RT. All authors read and approved the final version of the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

Some restrictions will apply to accessing the data for this study. All relevant aggregated data are within the paper and the supporting information files. Individual data cannot be made public in compliance with the protocol approved by the research ethics board to respect participant privacy. Researchers can request approval to access deidentified data from the Instituto Nacional de Saúde, Timor-Leste (1545MS-INS/DE/X/2019) and University of New South Wales Ethics Board, Australia (HC190140).

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