The impact of intensive versus standard anthelminthic treatment on allergy-related outcomes, helminth infection intensity and helminth-related morbidity in Lake Victoria fishing communities, Uganda: results from the LaVIISWA cluster randomised trial

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SUMMARY

In a cluster-randomised trial of intensive versus standard anthelminthic treatment, intensive treatment reduced *Schistosoma mansoni* intensity and hookworm prevalence, but had no effect on atopy, allergy-related disease or helminth-related pathology. Additional interventions are required to reduce transmission in schistosomiasis hot-spots.

Running title: Anthelminthic treatment and allergy

ABSTRACT

Background

Allergy-related disease is increasing in low-income countries. Parasitic helminths, common in these settings, may be protective. We hypothesised that intensive community-wide anthelminthic mass drug administration (MDA) would increase allergy-related diseases, while reducing helminth-related morbidity.

Methods

In an open, cluster-randomised trial (ISRCTN47196031), we randomised 26 high-schistosomiasis-transmission fishing villages, Lake Victoria, Uganda, in a 1:1 ratio to receive community-wide intensive (quarterly single-dose praziquantel plus albendazole daily for three days) or standard (annual praziquantel plus six-monthly single-dose albendazole) MDA. Primary outcomes were recent wheeze, skin prick test positivity (SPT) and allergen-specific immunoglobulin E (asIgE) after three years' intervention. Secondary outcomes included helminths, haemoglobin and hepatosplenomegaly.

Results

The outcome survey comprised 3350 individuals. Intensive MDA had no effect on wheeze, SPT or asIgE (risk ratios (95% confidence intervals): 1.11 (0.64,1.93), 1.10 (0.85,1.42) and 0.96 (0.82,1.12), respectively). Intensive MDA reduced *S. mansoni* infection intensity: prevalence from Kato-Katz examination of one stool sample was 23% versus 39% (RR 0.70 (0.55,0.88)), but the more-sensitive urine circulating cathodic antigen test remained positive in 85% participants in both trial arms. Hookworm prevalence was 8% versus 11% (RR 0.55 (0.31,1.00)). There were no differences in anaemia or hepatospenomegaly between trial arms.

Conclusions

Despite reductions in *S. mansoni* intensity and hookworm prevalence, intensive MDA had no effect on atopy, allergy-related disease or helminth-related pathology. This could be due to sustained low-intensity infections, thus a causal link between helminths and allergy outcomes cannot be discounted. Intensive community-based MDA has limited impact in high-schistosomiasis-transmission fishing communities, in the absence of other interventions.

Key words: Helminths, *Schistosoma mansoni*, mass drug administration, allergy-related disease, Africa.

INTRODUCTION

The prevalence of allergy-related diseases (ARD) such as eczema, rhinitis and asthma increased rapidly in high-income countries in the twentieth century [1] and is now increasing in tropical, low-income countries (LICs) [2]. Nevertheless, populations in LICs, particularly in rural settings, remain relatively protected [3]. Understanding this phenomenon is crucial to elucidating causes, and improving prevention, of ARD.

By contrast, LICs carry the largest burden of parasitic helminth infections: these are associated with some severe and much subtle morbidity [4, 5]. Major anthelminthic Mass Drug Administration (MDA) has taken place in the last decade but, although prevention of severe helminth-induced morbidity is important, wider benefits [6], and sustainability of helminth control by MDA [7, 8], have been questioned.

Certain helminth antigens are highly homologous to allergens; immunoglobulin (Ig)-E and the atopic pathway are presumed to have evolved to protect mammals against such organisms [9]. Parasitic helminths must modulate such responses to survive within mammalian hosts. Animal and human epidemiological and *in vitro* studies indicate that, through by-stander effects of such immunomodulation, chronic helminth infection protects against atopy and ARD [10]. If helminths protect against ARD, MDA programmes may adversely affect these outcomes. Observational studies, many of which indicate an inverse association between helminths and ARD, are subject to confounding and reverse causation; therefore several groups have investigated effects of anthelminthic treatment on ARD in clinical trials. Some studies show increased atopy after anthelminthic intervention, but two large, school-based, individually-randomised intervention trials focussing on soil-transmitted helminths (STH) reported no effect on atopy or ARD [11, 12]. A recent household-randomised trial of intensive albendazole for STH showed no effect on ARD but upregulated pro-inflammatory responses, and reduced immunoregulatory molecules [13].

East African fishing communities bear an intense schistosomiasis burden [14]. During *Schistosoma mansoni* infection, adult worms reside in mesenteric blood vessels and eggs are excreted through intestinal mucosa, causing intestinal and tissue (notably liver) pathology [5]. *Schistosoma* infection has shown even stronger inverse associations with atopy than STH [15] and there is evidence of increased SPT reactivity with treatment [16], but no large-scale randomised trial on allergy-related effects of intensively treating schistosomiasis has been conducted.

We undertook the Lake Victoria Island Intervention Study on Worms and Allergy-related diseases (LaVIISWA; ISRCTN47196031) [17], a cluster-randomised trial of extended (three-year) intensive versus standard anthelminthic intervention, to assess the causal role of helminths in allergy-related outcomes and the benefits of intensive intervention for helminth-related morbidity in a schistosomiasis "hot-spot".

METHODS

Design and setting

This was a two-arm, open, cluster-randomised trial of intensive versus standard anthelminthic treatment conducted among fishing villages in the Koome islands, Lake Victoria, Uganda between September 2012 and August 2016. The protocol has been published [17]. Twenty-six villages were randomised 1:1 to intensive or standard intervention. Village-level cluster-randomisation aimed to minimise contamination from re-infection by untreated neighbours. Before the study, annual praziquantel treatment was offered to these communities, but hampered by logistics. In our baseline survey, 17% participants reported treatment in the past year [17].

Interventions

Standard intervention (Uganda Ministry of Health (MoH) guidelines) was annual single-dose praziquantel 40mg/kg (Cipla; CSPC OUYI Pharmaceuticals, India; AGOG Pharma, India), estimated by height-pole, to community members ≥94cm plus six-monthly single-dose albendazole 400mg (CSPC OUYI Pharmaceuticals, India; AGOG Pharma, India; Medreich, India) to all aged ≥1-year. Intensive intervention was quarterly single-dose praziquantel 40mg/kg (estimated by extended height-pole for individuals ≥60cm to allow treatment of younger children) [18] plus quarterly triple-dose albendazole (400mg daily, three days) to all aged ≥1-year. Pregnant women were included in both arms, receiving single-dose albendazole [19, 20].

Treatment, distributed house-to-house in collaboration with the Uganda MoH Vector Control Division, was directly observed and documented against household registers, with the exception of post-day-one albendazole in the intensive arm.

Participants and surveys

Leaders of all 27 Koome fishing villages gave written consent for village participation. Allocated interventions were given to all community members (of eligible age and height) unless absent, sick or refused.

Household-based surveys were conducted at baseline [21] and after three years' intervention. All primary, and most secondary, outcomes were assessed in both baseline and outcome surveys. Smaller surveys were conducted at years one and two to assess helminth trends (Supplementary Figure). Separate random household samples were selected for each survey (overlap was possible). There was no individual participant follow-up. Surveys were conducted immediately prior to respective quarterly treatments.

Household registers were updated before each survey. Villages generally comprised an intensely populated centre and scattered periphery. Peripheral households were excluded from surveys to avoid contamination from neighbouring villages, but received allocated interventions.

Baseline survey methods (previously reported) were similar to the three-year outcome survey described below [21]. For interim surveys, stool and blood samples were collected from community members selected using a two-stage method: one person was randomly selected from each of 15 randomly selected households per village. For the three-year survey, 70 households per village were randomly selected using a Stata program (StataCorp, College Station, USA). In selected households, all members ≥1-year were invited to participate. Household heads gave permission for household participation, and details (age, sex) of all members. Written informed consent was obtained from all adults and emancipated minors and from parents/guardians for children, with additional assent from children ≥8 years. For each participant, a questionnaire was completed; examination and SPT performed; and blood, urine and one stool sample obtained. Abdominal ultrasonography was performed on children.

Outcomes

Primary outcomes were recent (last 12 months) self-reported wheeze stratified by age (<5 years, ≥5 years), SPT positivity to mites (*Dermatophagoides* mix, *Blomia tropicalis*) and German cockroach (*Blattella germanica*), and allergen-specific IgE (asIgE) to *Dermatophagoides* and German cockroach (common allergens in Uganda [22]). Secondary outcomes were visible flexural dermatitis (assessed using standardised procedures), helminth infections, haemoglobin, growth (height-for-age (<20 years), weight-for-age (<11 years), weight-for-height (<6 years) z-scores) and hepatosplenomegaly (by palpation). An additional secondary outcome, schistosomiasis-related liver and spleen morbidity assessed by abdominal ultrasonography (<18 years), was included after trial interventions commenced when additional funding became available. Exploratory outcomes were recent urticaria and rhinitis. For logistical reasons we could not provide infant vaccines ourselves, or obtain post-immunisation samples at consistent timepoints, so planned vaccine response secondary outcomes are not reported. Details on outcome ascertainment are provided (Supplementary Methods).

Randomisation

At a public ceremony, one village was randomly selected for piloting while 26 were randomised 1:1, using restricted randomisation to balance village size, prior praziquantel treatment and distance from sub-county health centre [17] (Supplementary Methods).

Statistical methods

For the outcome survey, we planned to sample 1540 individuals per arm (Supplementary Methods). Data were analysed using Stata v14.0. Baseline characteristics were tabulated. Characteristics of survey participants were compared with those of non-participants by chi-squared tests. Treatment uptake was calculated, by village and treatment round, as the number of people receiving treatment divided by the total number of residents.

Trial analyses were done at cluster-level. Crude and adjusted analyses (adjusting for sex, age and the corresponding baseline summary measure of the outcome, where available) were performed. For binary outcomes, risk ratios (RR) were calculated as the mean of the intensive arm cluster proportions divided by the mean in the standard arm, with 95% confidence intervals (CI) calculated using a Taylor series approximation for the standard error, and p-values from unpaired t-tests. Where the distribution of cluster proportions was skewed, log-cluster proportions were compared and results back-transformed. A two-stage approach was used for adjusted analyses [23] (Supplementary Methods).

For continuous outcomes, intervention effects were quantified as differences in mean outcome between trial arms, with 95% CIs calculated using the t-distribution. Non-normally distributed continuous outcomes were log-transformed and results back-transformed to obtain geometric mean ratios. For ordered categorical outcomes, a proportional-odds model was used.

Trial analyses were conducted in two populations: the primary analysis population ("intention-to-treat") included all individuals. The secondary analysis population comprised all individuals who had lived in their village throughout (or were born into their village during) the intervention period ("per protocol").

Using a cluster-level approach [24], we conducted post-hoc subgroup analyses by age group (<4 years, ≥4 years) for primary outcomes, to assess whether intervention effects differed among those exposed to differential anthelminthic interventions from birth.

Ethics statement

Ethical approval was given by the Uganda Virus Research Institute (GC127), Uganda National Council for Science and Technology (HS 1183) and London School of Hygiene & Tropical Medicine (6187).

RESULTS

Participants and intervention uptake

Characteristics assessed in the baseline survey (October 2012-July 2013), were balanced between trial arms, with the exception that, compared to villages in the intensive arm ("intensive villages"), villages in the standard arm ("standard villages") had fewer public toilets but contained more households with private toilets [17].

Figure 1 summarises treatment uptake. Both praziquantel and albendazole uptake increased during the trial. Mean uptake per round was 63% for praziquantel and 64% for albendazole (intensive villages), compared to 56% and 73% (standard villages). In standard villages, albendazole uptake was lower in treatment rounds where praziquantel treatment was also given. Reported receipt of ≥1dose of praziquantel in the preceding year was higher in intensive, compared to standard, villages (93% versus 75%). Reported receipt of ≥1 dose of albendazole was universally high (99% versus 98%).

Between September 2015 and August 2016, 70 households from each village were randomly selected for the outcome survey (Figure 2); 84 (5%) refused, 17 (1%) consented but no demographic data were captured; for 300 (17%) no members could be contacted. The remaining 1419 participating households contained 3566 residents aged ≥1-year. Overall, 3350 (94%) household members provided data for at least one primary outcome (recent wheeze 3323 (99%), SPT 3037 (91%), IgE 2955 (88%)), with numbers balanced between trial arms (Figure 2). Further details of participant characteristics are provided (Supplementary Material).

Outcome survey participant characteristics were comparable between trial arms (Table 1). Only eight villages had access to any non-lake water supply, with public toilets available in 11 villages, and private toilet access limited. Participant median age was 24 years (IQR: 8-34); 52% were male. Most participants (71%) had lived in their village throughout the trial. Migration between trial arms was low (1.5%). Adult HIV prevalence was 22%; reported maternal history of allergy, eczema or asthma was 16%.

Impact of intensive versus standard anthelminthic treatment on primary outcomes

Prevalence of wheeze among ≥5-year-olds was 3%, with little difference between trial arms (Table 2). Nine individuals <5-years reported wheeze; no formal analysis was done for this outcome. Regarding atopy, 19% participants had a positive SPT to ≥1 allergen. Of those tested using ImmunoCAP, 54% were positive (IgE>0.35kUa/L) for either cockroach or dust mite allergens. ELISA and ImmunoCAP results were positively correlated for both dust mites and cockroach (Spearman's correlation coefficient 0.32 and 0.29, respectively). There was no effect of intensive versus standard treatment on atopy (by SPT or IgE; Table 2). For all primary outcomes, there remained little evidence of a difference between trial arms in the "per protocol" analysis (Supplementary Table 1), or among age-groups (Supplementary Table 2), although RR for SPT responses to individual allergens increased in both the "per protocol" analysis, and in children<4 years.

Impact of intensive versus standard anthelminthic treatment on secondary and exploratory outcomes

Schistosoma mansoni infection prevalence was lower in intensive villages when assessed by stool Kato-Katz (23% versus 39%, adjusted RR 0.70; 95%CI: 0.55-0.88; Table 3) and stool PCR (39% versus 60%, adjusted RR 0.76; 95%CI: 0.65-0.88), but urine CCA positivity remained high and similar across trial arms (both 85%; Table 3), indicating that intensive treatment was more effective than standard in reducing heavy intensity *Schistosoma* infections, particularly apparent in younger age groups, but had little impact on light infection prevalence (Figure 3A). *Schistosoma* infection was lower in both trial arms, compared to baseline: 49% and 23% pre- and post-intervention in intensive, 56% and 39% in standard. Interim survey data suggested a greater initial reduction in intensive villages, which then plateaued, and a gradual reduction in standard villages (Figure 3B). STH prevalence was relatively low. Intensive treatment reduced hookworm prevalence; no significant reductions were seen for other nematodes (Table 3). There was no impact of intensive versus standard treatment on anthropometric or clinical outcomes, including hepatosplenomegaly assessed by palpation (Table 3) or ultrasound (among children; Supplementary Table 3). The "per protocol" analysis did not yield any hitherto unseen differences (Supplementary Table 4).

Serious adverse events

77,739 praziquantel treatments and 102,219 albendazole treatments were given. Four serious adverse events were reported, all among adults, within two days of treatment, two in each trial arm: gastrointestinal symptoms leading to hospitalisation (1) or requiring intravenous fluids (1); abdominal pain and vaginal bleeding in a non-pregnant woman (1); vaginal bleeding one day after treatment in a pregnant woman, followed by delivery three days later (probably premature) and subsequent neonatal death (1). Clinic records suggested that this last woman had concurrent malaria but this remained unconfirmed.

DISCUSSION

We report the first trial to address community-level effects of intensive anthelminthic MDA in a high *Schistosoma mansoni* transmission setting. After three years, we found no effect of intensive, compared to standard, intervention on allergy-related or helminth-associated disease outcomes. Intensive, compared to standard, praziquantel achieved a substantial reduction in *S. mansoni* intensity, most marked after one year, but infection remained almost universal. Intensive, compared to standard, albendazole achieved a modest reduction in hookworm prevalence, but had little impact on *Trichuris* or *Strongyloides*.

Prevalence of wheeze was lower than anticipated based on previous reports [25], limiting power for this outcome. Understanding of "wheeze" in study communities was poor; there are no words for wheeze or asthma in the vernacular and asthma is rare. That said, there was no effect of intensive intervention on wheeze, and no increase in wheeze during the intervention (5% at baseline [13], 3% after three years). These results provide reassurance that anthelminthic MDA is unlikely to have an immediate adverse effect on asthma among high-schistosomiasis-transmission communities, although no conclusions can be drawn on the impact of effective, universal, *S. mansoni* removal.

SPT positivity was common. There was no increase in SPT positivity during the intervention (19% at baseline [13], 18% and 20% in the standard and intensive arms respectively after three years). There was a suggestion, especially in the "per protocol" analysis and in under-four-year-olds, that SPT responses increased with intensive treatment. This could be a chance finding, since a substantial number of (planned) statistical tests were conducted. This warrants more detailed investigation as it may presage emergence of increased atopy and ARD when helminth infections are more completely cleared. The effect of treatment may have differed based on pre-treatment infection intensity [26]. We could not assess this hypothesis because our study was not a cohort of individual subjects.

Despite our emphasis on schistosomiasis, and on long-term, community-based intervention, our results accord with previous, shorter-term trials focussing on STH [10]. However, it seems premature to conclude that high helminth prevalence has no causal link with low ARD prevalence in LICs, given strong effects and demonstrated mechanisms in animal models and experiments using human samples *in vitro* [27].

The most obvious explanation for a lack of impact on allergy-related (or helminth-associated) disease is failure to clear helminth infections. All villages were continuously exposed to *S. mansoni*-infested lake water because of lack of alternative safe water, involvement in fishing and open defaecation due to scarcity of latrines. Although single- and first-dose treatment were directly observed, compliance was imperfect; albendazole uptake in the standard arm was lower in rounds where praziquantel was given, indicating that villagers were averse to praziquantel side effects. Furthermore, we cannot rule out the possible role of reduced drug efficacy [28, 29]. However, as a differential effect on helminth intensity was achieved, particularly for schistosomiasis, our results cast doubt on the extent to which intensity reduction (without elimination) substantially modifies overall immunological or pathological effects in high-schistosomiasis-transmission settings.

Other factors contributing to lack of impact on allergy-related outcomes may include long-term immunological effects of helminth exposure through persistence of antigen, or through epigenetic changes in immunological pathways [30]. Also, in tropical, low-income settings, numerous other exposures, including immunomodulating infections such as malaria, exposure to dirt and domestic animals, or the microbiome profile, may impact allergy-related outcomes, such that modifying helminth exposure alone may have limited impact [31].

A recent meta-analysis examined effects of treating schistosomiasis on related morbidity [32]. The results indicated wide-ranging benefits, with increased impact when egg reduction rates were greatest and, for anaemia and chronic morbidities, when treatments were repeated over periods of greater than 24 months. Thus we were disappointed that, despite differential reduction in schistosome intensity, we found no evidence that three years' intensive (compared to standard) intervention achieved improvement in any morbidity measure. This adds to the evidence base showing limited effects of MDA on such outcomes at community-level. We identified surprisingly little severe *Schistosoma*-related morbidity in this community, despite intense infection, consistent with earlier work from Lake Victoria communities; it is possible that intensive intervention would have greater benefit in settings (such as Lake Albert) where severe pathology is more common [33].

Our experience emphasises that MDA may struggle to eliminate helminths as a public health problem, especially in high-transmission environments. The substantial decline in *S. mansoni* infection (by Kato-Katz) achieved in year-one led us to hope that intensive intervention could make an important contribution to schistosomiasis control in these challenging "hot-spots". The subsequent plateau and persistent infection (by CCA) were disheartening. This phenomenon (a large drop in prevalence followed by a subsequent plateau) has also been reported in Kenyan districts bordering Lake Victoria

[34]. Besides reinfection, the possibility of selection for praziquantel-resistant or tolerant strains is of concern [35]. A radically different approach, with complementary interventions including improved water supply and sanitation, behaviour change and vector control is needed: and an effective vaccine against schistosomiasis [36].

Observational analyses addressing effects of helminths remain limited by confounding by poverty and environment. Our strategy aimed to pinpoint helminth effects by randomising their treatment, but was constrained by difficulties in achieving removal. Trials designed so that helminths are cleared, in settings where re-infection can be avoided, and with substantial follow-up, are needed for a full understanding of the risks and benefits of "de-worming".

NOTES

AUTHOR CONTRIBUTIONS

AME conceived the study. AME, ELW, ET, RES, MN, and HM participated in designing the trial. RES, AME, MN, GO'H, CZ, RK, J Kaweesa, E Nakazibwe, JT and FM led and participated in the surveys. GO, PK, EA and E Niwagaba ran the field laboratory, while GN and J Kabagenyi, participated in establishing and conducting immunological assays, PCR. JV trained and assisted in stool PCR. RvR contributed to testing of allergen-specific responses. MA monitored the study. LL managed the database. ELW, SN and RHS conducted the statistical analysis. RES, GN, RHS, ELW, and AME drafted the manuscript and all authors reviewed and contributed to it. All authors read and approved of the final version of the manuscript.

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DISCLAIMER

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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CONFLICT OF INTEREST STATEMENT

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REFERENCES

1. Anderson HR, Gupta R, Strachan DP, Limb ES. 50 years of asthma: UK trends from 1955 to 2004. Thorax. 2007;62(1):85-90. doi: 10.1136/thx.2006.066407. PubMed PMID: 17189533; PubMed Central PMCID: PMC2111282.

2. Pawankar R. Allergic diseases and asthma: a global public health concern and a call to action. The World Allergy Organization journal. 2014;7(1):12. doi: 10.1186/1939-4551-7-12. PubMed PMID: 24940476; PubMed Central PMCID: PMC4045871.

3. Nicolaou N, Siddique N, Custovic A. Allergic disease in urban and rural populations: increasing prevalence with increasing urbanization. Allergy. 2005;60(11):1357-60. doi: 10.1111/j.1398-9995.2005.00961.x. PubMed PMID: 16197466.

4. Pullan RL, Smith JL, Jasrasaria R, Brooker SJ. Global numbers of infection and disease burden of soil transmitted helminth infections in 2010. Parasit Vectors. 2014;7:37. doi: 10.1186/1756-3305-7-37. PubMed PMID: 24447578; PubMed Central PMCID: PMCPMC3905661.

5. Colley DG, Bustinduy AL, Secor WE, King CH. Human schistosomiasis. Lancet. 2014;383(9936):2253-64.

6. Allen T, Parker M. Deworming delusions? Mass drug administration in East African schools. Journal of biosocial science. 2016;48 Suppl 1:S116-47. Epub 2016/07/20. doi: 10.1017/s0021932016000171. PubMed PMID: 27428063.

7. Gurarie D, Yoon N, Li E, Ndeffo-Mbah M, Durham D, Phillips AE, et al. Modelling control of Schistosoma haematobium infection: predictions of the long-term impact of mass drug administration in Africa. Parasit Vectors. 2015;8:529. Epub 2015/10/23. doi: 10.1186/s13071-015-1144-3. PubMed PMID: 26489408; PubMed Central PMCID: PMCPMC4618728.

8. Phillips AE, Gazzinelli-Guimaraes PH, Aurelio HO, Ferro J, Nala R, Clements M, et al. Assessing the benefits of five years of different approaches to treatment of urogenital schistosomiasis: A SCORE project in Northern Mozambique. PLOS Neglected Tropical Diseases. 2017;11(12):e0006061. doi: 10.1371/journal.pntd.0006061.

9. Fitzsimmons CM, Dunne DW. Survival of the fittest: allergology or parasitology? Trends in parasitology. 2009;25(10):447-51. Epub 2009/09/12. doi: 10.1016/j.pt.2009.07.004. PubMed PMID: 19744885.

10. Wammes LJ, Mpairwe H, Elliott AM, Yazdanbakhsh M. Helminth therapy or elimination: epidemiological, immunological, and clinical considerations. Lancet Infect Dis. 2014;14(11):1150-62. doi: 10.1016/S1473-3099(14)70771-6. PubMed PMID: 24981042.

11. Cooper PJ, Chico ME, Vaca MG, Moncayo AL, Bland JM, Mafla E, et al. Effect of albendazole treatments on the prevalence of atopy in children living in communities endemic for geohelminth parasites: a cluster-randomised trial. Lancet. 2006;367(9522):1598-603. Epub 2006/05/16. doi: 10.1016/s0140-6736(06)68697-2. PubMed PMID: 16698413.

12. Flohr C, Tuyen LN, Quinnell RJ, Lewis S, Minh TT, Campbell J, et al. Reduced helminth burden increases allergen skin sensitization but not clinical allergy: a randomized, double-blind, placebo-controlled trial in Vietnam. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical

Immunology. 2010;40(1):131-42. Epub 2009/09/18. doi: 10.1111/j.1365-2222.2009.03346.x. PubMed PMID: 19758373.

13. Wammes LJ, Hamid F, Wiria AE, May L, Kaisar MM, Prasetyani-Gieseler MA, et al. Community deworming alleviates geohelminth-induced immune hyporesponsiveness. Proceedings of the National Academy of Sciences of the United States of America. 2016;113(44):12526-31. Epub 2016/11/03. doi: 10.1073/pnas.1604570113. PubMed PMID: 27791067; PubMed Central PMCID: PMCPMC5098677.

14. Kabatereine NB, Brooker S, Tukahebwa EM, Kazibwe F, Onapa AW. Epidemiology and geography of Schistosoma mansoni in Uganda: implications for planning control. Tropical medicine & international health : TM & IH. 2004;9(3):372-80. Epub 2004/03/05. PubMed PMID: 14996367.

15. van den Biggelaar AH, van Ree R, Rodrigues LC, Lell B, Deelder AM, Kremsner PG, et al. Decreased atopy in children infected with Schistosoma haematobium: a role for parasite-induced interleukin-10. Lancet. 2000;356(9243):1723-7. Epub 2000/11/30. doi: 10.1016/s0140-6736(00)03206-2. PubMed PMID: 11095260.

16. van den Biggelaar AH, Rodrigues LC, van Ree R, van der Zee JS, Hoeksma-Kruize YC, Souverijn JH, et al. Long-term treatment of intestinal helminths increases mite skin-test reactivity in Gabonese schoolchildren. The Journal of infectious diseases. 2004;189(5):892-900. Epub 2004/02/21. doi: 10.1086/381767. PubMed PMID: 14976607.

17. Nampijja M, Webb EL, Kaweesa J, Kizindo R, Namutebi M, Nakazibwe E, et al. The Lake Victoria Island Intervention Study on Worms and Allergy-related diseases (LaVIISWA): study protocol for a randomised controlled trial. Trials. 2015;16:187. Epub 2015/04/24. doi: 10.1186/s13063-015-0702-5. PubMed PMID: 25902705; PubMed Central PMCID: PMC4413531.

18. Sousa-Figueiredo JC, Betson M, Stothard JR. Treatment of schistosomiasis in African infants and preschool-aged children: downward extension and biometric optimization of the current praziquantel dose pole. International health. 2012;4(2):95-102. Epub 2012/08/10. doi: 10.1016/j.inhe.2012.03.003. PubMed PMID: 22876272; PubMed Central PMCID: PMCPMC3407873.

19. WHO. Report of the WHO informal consultation on hookworm infection and anaemia in girls and women. Report. Geneva: WHO, Schistosomiasis and Intestinal Parasites Unit DoCoTD; 1994 5-7 December. Report No.: Contract No.: WHO/CTD/SIP/96.1.

20. WHO. Report of the WHO informal consultation on the use of praziquantel during pregnancy/lactation and albendazole/mebendazole in children under 24 months. Geneva, 8-9 April 2002. WHO/CDS/CPE/PVC/2002.4. 2002.

21. Webb EL, Nampijja M, Kaweesa J, Kizindo R, Namutebi M, Nakazibwe E, et al. Helminths are positively associated with atopy and wheeze in Ugandan fishing communities: results from a cross-sectional survey. Allergy. 2016;71(8):1156-69. doi: 10.1111/all.12867. PubMed PMID: 26918891; PubMed Central PMCID: PMC4949563.

22. Mpairwe H, Muhangi L, Ndibazza J, Tumusiime J, Muwanga M, Rodrigues LC, et al. Skin prick test reactivity to common allergens among women in Entebbe, Uganda. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2008;102(4):367-73. doi: 10.1016/j.trstmh.2008.01.017. PubMed PMID: PMC2628422.

23. Hayes RJ, Moulton LH. Cluster randomised trials. N. K, Morgan BJT, Wikle CK, P. vdH, editors. Boca Raton: CRC Press, Taylor & Francis Group; 2009 2009.

24. Cheung YB, Jeffries D, Thomson A, Milligan P. A simple approach to test for interaction between intervention and an individual-level variable in community randomized trials. Trop Med Int Health. 2008;13(2):247-55. Epub 2008/02/29. doi: 10.1111/j.1365-3156.2007.01997.x. PubMed PMID: 18304272.

25. Asher MI, Montefort S, Bjorksten B, Lai CK, Strachan DP, Weiland SK, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. Lancet. 2006;368(9537):733-43. Epub 2006/08/29. doi: 10.1016/s0140-6736(06)69283-0. PubMed PMID: 16935684.

26. Rujeni N, Nausch N, Bourke CD, Midzi N, Mduluza T, Taylor DW, et al. Atopy is inversely related to schistosome infection intensity: a comparative study in Zimbabwean villages with distinct levels of Schistosoma haematobium infection. International archives of allergy and immunology. 2012;158(3):288-98. Epub 2012/03/09. doi: 10.1159/000332949. PubMed PMID: 22398631; PubMed Central PMCID: PMCPMC3398828.

27. Maizels RM, McSorley HJ. Regulation of the host immune system by helminth parasites. The Journal of allergy and clinical immunology. 2016;138(3):666-75. Epub 2016/08/02. doi: 10.1016/j.jaci.2016.07.007. PubMed PMID: 27476889; PubMed Central PMCID: PMCPMC5010150.

28. Bergquist R, Utzinger J, Keiser J. Controlling schistosomiasis with praziquantel: How much longer without a viable alternative? Infectious diseases of poverty. 2017;6(1):74. Epub 2017/03/30. doi: 10.1186/s40249-017-0286-2. PubMed PMID: 28351414; PubMed Central PMCID: PMC5371198.

29. Vale N, Gouveia MJ, Rinaldi G, Brindley PJ, Gartner F, Correia da Costa JM. Praziquantel for Schistosomiasis: Single-Drug Metabolism Revisited, Mode of Action, and Resistance. Antimicrobial agents and chemotherapy. 2017;61(5). Epub 2017/03/08. doi: 10.1128/AAC.02582-16. PubMed PMID: 28264841; PubMed Central PMCID: PMC5404606.

30. Wenzel MA, Piertney SB. Fine-scale population epigenetic structure in relation to gastrointestinal parasite load in red grouse (Lagopus lagopus scotica). Molecular ecology. 2014;23(17):4256-73. Epub 2014/06/20. doi: 10.1111/mec.12833. PubMed PMID: 24943398; PubMed Central PMCID: PMCPMC4282444.

31. Smits HH, Hiemstra PS, Prazeres da Costa C, Ege M, Edwards M, Garn H, et al. Microbes and asthma: Opportunities for intervention. The Journal of allergy and clinical immunology. 2016;137(3):690-7. Epub 2016/03/08. doi: 10.1016/j.jaci.2016.01.004. PubMed PMID: 26947981.

32. Andrade G, Bertsch DJ, Gazzinelli A, King CH. Decline in infection-related morbidities following drug-mediated reductions in the intensity of Schistosoma infection: A systematic review and meta-analysis. PLoS Negl Trop Dis. 2017;11(2):e0005372. Epub 2017/02/18. doi: 10.1371/journal.pntd.0005372. PubMed PMID: 28212414; PubMed Central PMCID: PMCPMC5333910.

33. Tukahebwa EM, Magnussen P, Madsen H, Kabatereine NB, Nuwaha F, Wilson S, et al. A very high infection intensity of Schistosoma mansoni in a Ugandan Lake Victoria Fishing Community is required for association with highly prevalent organ related morbidity. PLoS Negl Trop Dis. 2013;7(7):e2268. Epub 2013/08/13. doi: 10.1371/journal.pntd.0002268. PubMed PMID: 23936559; PubMed Central PMCID: PMCPMC3723538.

34. Karanja DMS, Awino EK, Wiegand RE, Okoth E, Abudho BO, Mwinzi PNM, et al. Cluster randomized trial comparing school-based mass drug administration schedules in areas of western Kenya with moderate initial prevalence of Schistosoma mansoni infections. PLoS neglected tropical diseases. 2017;11(10):e0006033. doi: 10.1371/journal.pntd.0006033.

35. Crellen T, Walker M, Lamberton PH, Kabatereine NB, Tukahebwa EM, Cotton JA, et al. Reduced Efficacy of Praziquantel Against Schistosoma mansoni Is Associated With Multiple Rounds of Mass Drug Administration. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2016;63(9):1151-9. Epub 2016/07/30. doi: 10.1093/cid/ciw506. PubMed PMID: 27470241; PubMed Central PMCID: PMCPMC5064161.

36. Alsallaq RA, Gurarie D, Ndeffo Mbah M, Galvani A, King C. Quantitative assessment of the impact of partially protective anti-schistosomiasis vaccines. PLoS Negl Trop Dis. 2017;11(4):e0005544. Epub 2017/04/15. doi: 10.1371/journal.pntd.0005544. PubMed PMID: 28410369; PubMed Central PMCID: PMCPMC5406007.

LaVIISWA trial team

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Table 1. Characteristics of outcome survey participants

	Standard arm		Intensive arm	
Cluster-level characteristics	**(n=13)**		**(n=13)**	
Mean no. of households per village (range)	307	(124-882)	289	(87-544)
Mean no. of participating households (range)	55	(48-63)	54	(48-64)
Mean no. of individuals resident in participating households (range)	137	(89-161)	137	(85-177)
Mean no. of individuals included in analysis (range)	129	(84-150)	129	(79-169)
Villages with any public toilets	5	38%	6	46%
Median no. of public toilets (range)	0	(0-16)	0	(0-20)
Median no. of private toilets (range)	8	(0-59)	3	(1-29)
Water supply other than lake	3	23%	5	38%
Piped water	2	67%	2	40%
River or open spring	1	33%	2	40%
Open well	0	0%	1	20%
Household-level characteristics	**(n=714)**		**(n=705)**	
Median no. of household members (IQR)	2	(1-3)	2	(1-3)
Individual-level characteristics	**(n=1675)**		**(n=1675)**	
Sex, male	881	53%	857	51%
Age in years, grouped				
0-4	283	17%	264	16%
5-9	173	10%	219	13%
10-14	66	4%	115	7%
15-19	102	6%	79	5%
20-24	212	13%	179	11%
25-29	239	14%	216	13%
30-34	198	12%	211	13%
35-39	175	10%	140	8%

40-44	86	5%	106	6%
45+	141	8%	146	9%
Place of birth (mv 9, 19)[a]				
This fishing village	439	26%	477	29%
Other fishing village	48	3%	20	1%
Other rural village	1021	61%	1002	61%
Town	127	8%	127	8%
City	31	2%	30	2%
Has remained in village during intervention period (mv 9, 19)	1190	71%	1170	71%
Has lived in other trial arm during intervention period (mv 9, 19)	18	1%	32	2%
Maternal history of allergic diseases (mv 9, 19)				
No history	1193	72%	1204	73%
History of asthma, eczema or allergies	258	15%	266	16%
Don't know	215	13%	186	11%
Paternal history of allergic diseases (mv 9, 19)				
No history	1248	75%	1244	75%
History of asthma, eczema or allergies	145	9%	155	9%
Don't know	273	16%	257	16%
Occupation, grouped by type (mv 8, 19)				
Child, not at school	289	17%	275	17%
Student	257	15%	345	21%
Housewife	120	7%	101	6%
Fishing or lake related	564	34%	467	28%
Shops, saloons, artisans, service providers	118	7%	102	6%
Bars, restaurants, food providers, entertainment	114	7%	103	6%
Agricultural, lumbering, charcoal	157	9%	201	12%
Professional	11	1%	19	1%
Unemployed	37	2%	43	3%

Treated with albendazole in the last 12 months (mv 360, 253)	1291	98%	1404	99%
Treated with praziquantel in the last 12 months (mv 355, 253)	989	75%	1318	93%
Malaria treatment with coartem (mv 190, 167)	708	42%	747	45%
Malaria positivity by blood smear (*P. falciparum*) (mv 213, 214)	50	3%	52	4%
Individuals aged 13 years and over	**(n=1176)**		**(n=1112)**	
Frequency of lake contact (mv 9, 19)				
Every day	911	78%	776	71%
Almost every day	126	11%	147	13%
Once a week	95	8%	124	11%
Once a month	30	3%	35	3%
Less than once a month	4	0%	10	1%
Never	1	0%	1	0%
Individuals aged 18 years and over	**(n=1116)**		**(n=1041)**	
HIV+ (mv 173, 176)	192	20%	198	23%
HIV+ on ART	90	47%	103	52%
HIV+ not on ART	93	48%	90	45%
HIV+ not known if receiving ART	9	5%	5	3%

[a] **Figures in parentheses indicate missing values in the standard and intensive arm, respectively**

Table 2. Impact of intensive versus standard anthelminthic treatment on primary outcomes

Outcome	n/N (%) / geometric mean		Unadjusted		Adjusted for outcome at baseline, age and sex[a]	
	Standard	Intensive	RR/GMR (95% CI)	p-value	RR/GMR (95% CI)	p-value
Wheeze (age≥5 years)[b]	44/1384 (3.2%)	43/1392 (3.1%)	1.06 (0.61, 1.87)	0.82	1.11 (0.64, 1.93)	0.69
Wheeze (age<5 years)	6/284 (2.1%)	3/264 (1.1%)				
Atopy (SPT)						
SPT positivity to any allergen	273/1514 (18.0%)	303/1523 (19.9%)	1.09 (0.83, 1.44)	0.51	1.10 (0.85, 1.42)	0.46
SPT positivity to *Dermatophagoides*	162/1514 (10.7%)	164/1523 (10.8%)	0.98 (0.72, 1.35)	0.92	1.00 (0.74, 1.36)	0.99
SPT positivity to *Blomia tropicalis*	102/1514 (6.7%)	127/1522 (8.3%)	1.26 (0.83, 1.90)	0.26	1.27 (0.85, 1.91)	0.22
SPT positivity to German cockroach	156/1513 (10.3%)	194/1522 (12.8%)	1.24 (0.87, 1.77)	0.20	1.22 (0.87, 1.71)	0.21
Atopy (IgE detected by ImmunoCAP)						
Dermatophagoides or cockroach positivity (>0.35kUa/L)	214/390 (54.9%)	210/390 (53.9%)	0.97 (0.83, 1.13)	0.67	0.96 (0.82, 1.12)	0.60
Dermatophagoides positivity (asIgE>0.35kUa/L)	134/390 (34.4%)	130/390 (33.3%)	0.95 (0.76, 1.20)	0.67	0.96 (0.77, 1.19)	0.68
German cockroach positivity (asIgE>0.35kUa/L)	201/390 (51.5%)	192/390 (49.2%)	0.94 (0.80, 1.11)	0.47	0.94 (0.79, 1.11)	0.42

Concentration of asIgE to *Dermatophagoides* (kUa/L)[c]	GM: 0.158	GM: 0.129	0.78 (0.51, 1.17)	0.22	0.77 (0.52, 1.13)	0.17
Concentration of asIgE to German cockroach (kUa/L)[c]	GM: 0.342	GM: 0.289	0.82 (0.55, 1.22)	0.31	0.81 (0.55, 1.20)	0.28
Atopy (IgE detected by in house ELISA)						
Concentration of asIgE to *Dermatophagoides*[d]	GM: 60.3	GM: 73.8	1.13 (0.36, 3.50)	0.83	1.17 (0.39, 3.51)	0.78
Concentration of asIgE to German cockroach[d]	GM: 72.4	GM: 161.0	1.98 (0.59, 6.63)	0.25	1.51 (0.45, 5.04)	0.49

[a]Atopy outcomes assessed by IgE were adjusted for age and sex only; [b]For this outcome, a natural log transformation was applied to village level proportions to correct skewed distributions and data in parentheses are geometric means of village proportions; [c]log10(+0.001) transformation at individual level; dlog10(+1) transformation at individual level; RR: risk ratio; GM: geometric mean; GMR: geometric mean ratio; CI: confidence interval

Table 3. Impact of intensive versus standard anthelminthic treatment on helminths, clinical outcomes, hepatosplenomegaly by palpation, and anthropometry

	n/N (%) / arithmetic mean		Unadjusted		Adjusted for outcome at baseline, age and sex	
Outcome	Standard	Intensive	RR/mean difference (95% CI)	p-value	RR/mean difference (95% CI)	p-value
Helminth infections						
Schistosoma mansoni, stool Kato Katz	523/1355 (38.6%)	323/1396 (23.1%)	0.64 (0.43, 0.94)	0.02	0.70 (0.55, 0.88)	0.003
Schistosoma mansoni, stool PCR	797/1353 (59.9%)	541/1394 (38.8%)	0.68 (0.52, 0.89)	0.007	0.76 (0.65, 0.88)	0.001
Schistosoma mansoni, urine CCA	1229/1444 (85.1%)	1216/1435 (84.7%)	0.99 (0.91, 1.08)	0.85	1.00 (0.93, 1.08)	0.93
Hookworm, stool PCR[a]	147/1353 (10.9%)	112/1394 (8.0%)	0.54 (0.28, 1.02)	0.06	0.55 (0.31, 1.00)	0.05
Strongyloides stercoralis, stool PCR	112/1353 (8.3%)	78/1394 (5.6%)	0.74 (0.50, 1.11)	0.14	0.78 (0.54, 1.14)	0.21
Trichuris trichiura, stool Kato Katza	137/1355 (10.1%)	108/1396 (7.7%)	0.91 (0.40, 2.09)	0.82	0.85 (0.48, 1.50)	0.55
Ascaris lumbricoides, stool Kato Katz	11/1355 (0.8%)	3/1396 (0.2%)				
Clinical outcomes						
Visible flexural dermatitis	1/1558 (0.1%)	4/1553 (0.3%)				
Haemoglobin	14.0	13.9	-0.06 (-0.37, 0.25)	0.70	0.00 (-0.24, 0.25)	0.97

Anthropometry						
Height-for-age z-score, age 1-19 years	-0.48	-0.49	-0.01 (-0.20, 0.19)	0.95	0.02 (-0.16, 0.20)	0.83
Weight-for-age z-score, age 1-10 years	-0.06	-0.17	-0.11 (-0.31, 0.09)	0.27	-0.05 (-0.23, 0.12)	0.52
Weight-for-height z-score, age 1-5 years	0.15	0.19	-0.09 (-0.43, 0.26)	0.62	-0.06 (-0.40, 0.28)	0.72
Hepatosplenomegaly, palpation						
Hepatomegaly, palpation	100/1546 (6.5%)	98/1546 (6.3%)	0.97 (0.71, 1.32)	0.83	0.96 (0.70, 1.32)	0.80
Splenomegaly, palpation	87/1549 (5.6%)	63/1547 (4.1%)	0.73 (0.43, 1.25)	0.20	0.70 (0.43, 1.15)	0.13
Hepatosplenomegaly, palpation[1]	22/1548 (1.4%)	14/1548 (0.9%)	0.85 (0.52, 1.39)	0.49	0.78 (0.47, 1.30)	0.33
Reported clinical outcomes (exploratory)						
Urticaria, last 12 months	162/1667 (9.7%)	172/1656 (10.4%)	1.06 (0.86, 1.30)	0.59	1.06 (0.88, 1.27)	0.51
Rhinitis, last 12 months	78/1667 (4.7%)	74/1656 (4.5%)	1.02 (0.73, 1.42)	0.92	1.00 (0.74, 1.36)	0.99

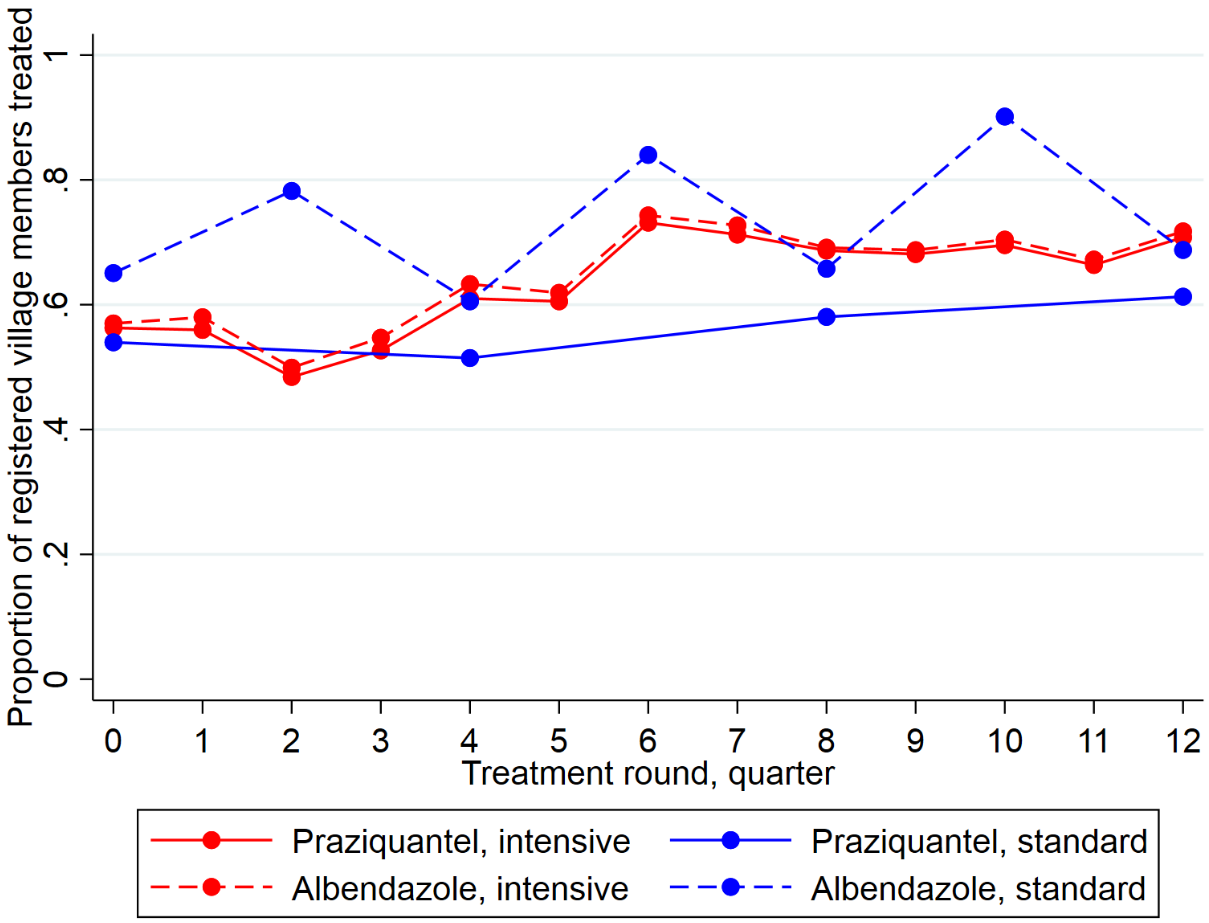
[a]For this outcome, a natural log transformation was applied to village level proportions to correct skewed distributions; RR: Risk Ratio; CI: confidence interval; CCA: circulating cathodic antigen; PCR: polymerase chain reaction

Figure 1. Praziquantel and albendazole treatment coverage, by trial arm and treatment round

Figure 2. Trial flowchart

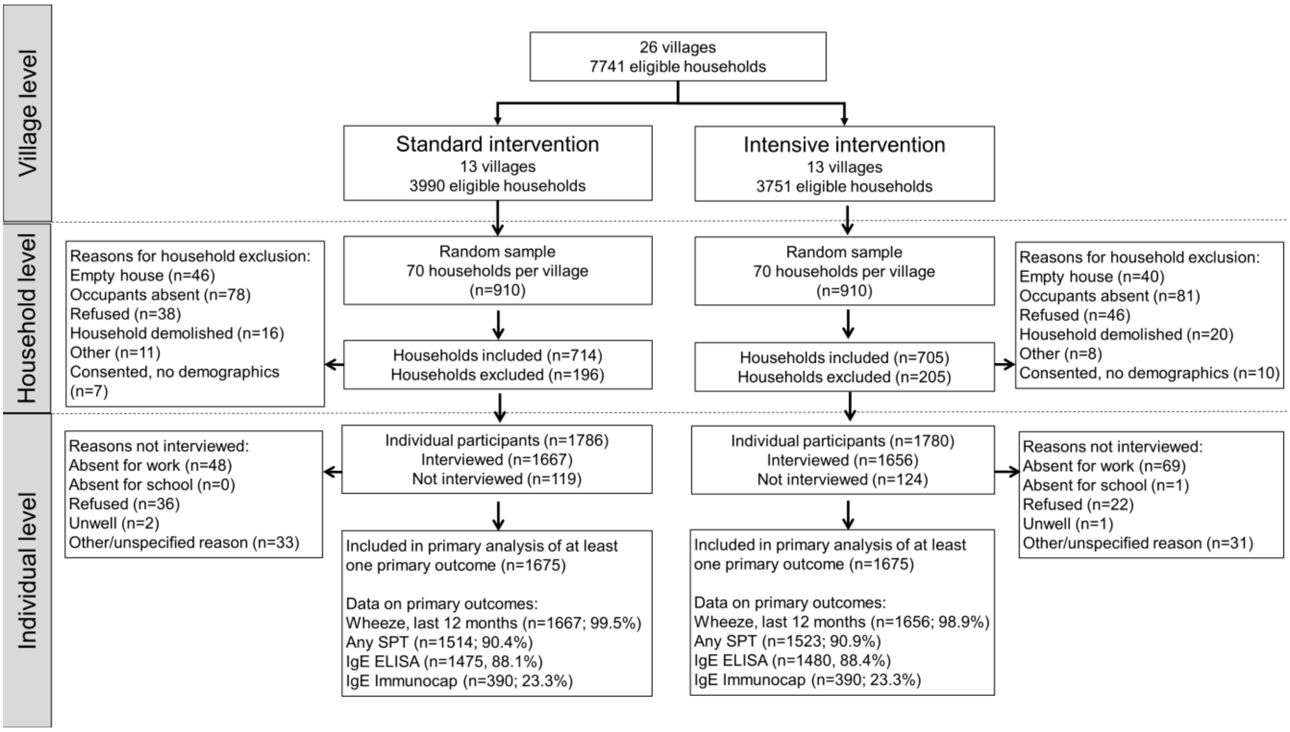
Figure 3. A: Intensity of schistosomiasis infection in the outcome survey, by age group and trial arm. B: Prevalence of schistosomiasis infection over time (pre-intervention baseline survey, interim survey at one year, interim survey at two years, outcome survey at three years), by trial arm. Panel A shows prevalence assessed by Kato Katz examination of a single stool sample (KK); polymerase chain reaction (PCR); and urine circulating cathodic antigen (CCA). Panel B shows the mean of village prevalences over time +/- 95% confidence intervals, assessed using KK analysis of a single stool sample (with duplicate slides) at each time point

Figure 1



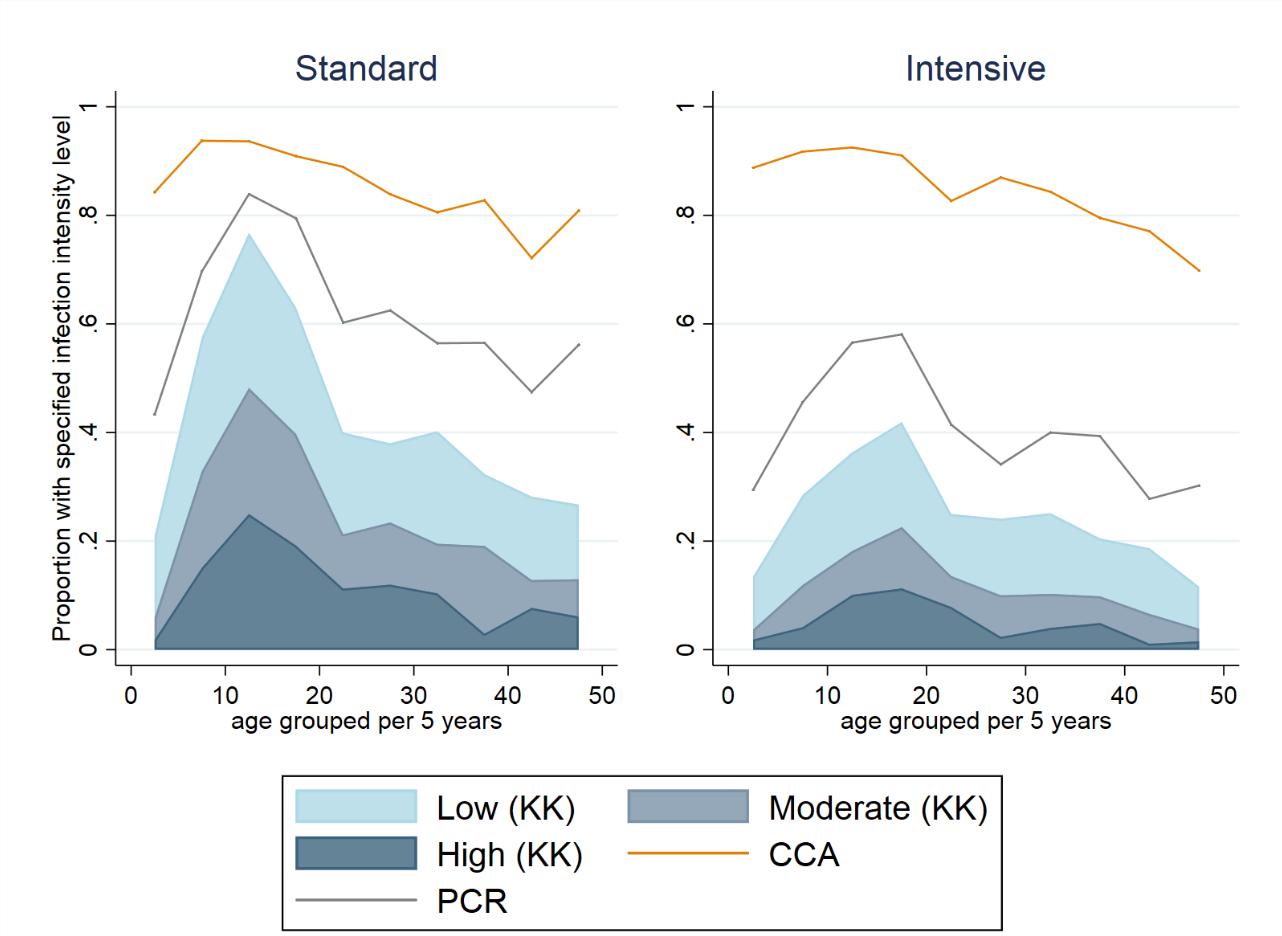
Proportion of registered village members treated
0
.2
.4
.6
.8
1
0
1
2
3
4
5
6
7
8
9
10
11
12
Treatment round, quarter
Praziquantel, intensive
Praziquantel, standard
Albendazole, intensive
Albendazole, standard

Figure 2



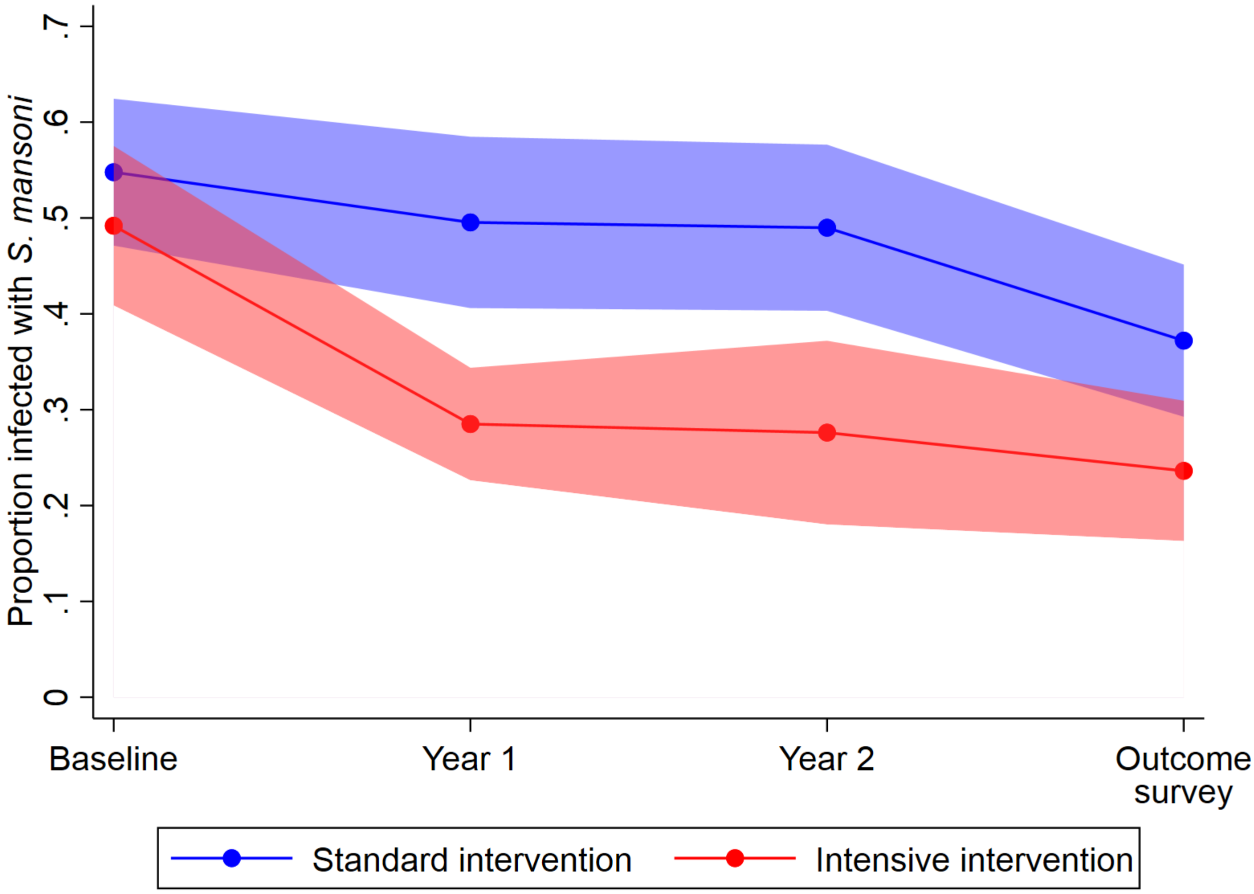
Village level
Household level
Individual level
26 villages
7741 eligible households
Standard intervention
13 villages
3990 eligible households
Intensive intervention
13 villages
3751 eligible households
Random sample
70 households per village
(n=910)
Random sample
70 households per village
(n=910)
Reasons for household exclusion:
Empty house (n=46)
Occupants absent (n=78)
Refused (n=38)
Household demolished (n=16)
Other (n=11)
Consented, no demographics (n=7)
Households included (n=714)
Households excluded (n=196)
Households included (n=705)
Households excluded (n=205)
Reasons for household exclusion:
Empty house (n=40)
Occupants absent (n=81)
Refused (n=46)
Household demolished (n=20)
Other (n=8)
Consented, no demographics (n=10)
Reasons not interviewed:
Absent for work (n=48)
Absent for school (n=0)
Refused (n=36)
Unwell (n=2)
Other/unspecified reason (n=33)
Individual participants (n=1786)
Interviewed (n=1667)
Not interviewed (n=119)
Individual participants (n=1780)
Interviewed (n=1656)
Not interviewed (n=124)
Reasons not interviewed:
Absent for work (n=69)
Absent for school (n=1)
Refused (n=22)
Unwell (n=1)
Other/unspecified reason (n=31)
Included in primary analysis of at least one primary outcome (n=1675)
Data on primary outcomes:
Wheeze, last 12 months (n=1667; 99.5%)
Any SPT (n=1514; 90.4%)
IgE ELISA (n=1475, 88.1%)
IgE Immunocap (n=390; 23.3%)
Included in primary analysis of at least one primary outcome (n=1675)
Data on primary outcomes:
Wheeze, last 12 months (n=1656; 98.9%)
Any SPT (n=1523; 90.9%)
IgE ELISA (n=1480, 88.4%)
IgE Immunocap (n=390; 23.3%)

Figure 3A



Standard
Intensive
Proportion with specified infection intensity level
0
.2
.4
.6
.8
1
0
10
20
30
40
50
age grouped per 5 years
Low (KK)
Moderate (KK)
High (KK)
CCA
PCR

Figure 3B



Proportion infected with S. mansoni
0
.1
.2
.3
.4
.5
.6
.7
Baseline
Year 1
Year 2
Outcome survey
Standard intervention
Intensive intervention