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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

Richard E Sanya* (Immunomodulation and Vaccines Programme, Medical Research Council/ Uganda Virus Research Institute and London School of Hygiene and Tropical Medicine Uganda Research Unit, Entebbe, Uganda; Department of Internal Medicine, College of Health Sciences, Makerere University, Kampala, Uganda)

Gyaviira Nkurunungi * (Immunomodulation and Vaccines Programme, Medical Research Council/ Uganda Virus Research Institute and London School of Hygiene and Tropical Medicine Uganda Research Unit, Entebbe, Uganda; Department of Clinical Research, London School of Hygiene and Tropical Medicine, London, United Kingdom)

Remy Hoek Spaans * (Immunomodulation and Vaccines Programme, Medical Research Council/ Uganda Virus Research Institute and London School of Hygiene and Tropical Medicine Uganda Research Unit, Entebbe, Uganda)

Margaret Nampijja (Immunomodulation and Vaccines Programme, Medical Research Council/ Uganda Virus Research Institute and London School of Hygiene and Tropical Medicine Uganda Research Unit, Entebbe, Uganda)

Geraldine O’Hara (Immunomodulation and Vaccines Programme, Medical Research Council/ Uganda Virus Research Institute and London School of Hygiene and Tropical Medicine Uganda Research Unit, Entebbe, Uganda; Department of Clinical Research, London School of Hygiene and Tropical Medicine, London, United Kingdom)
Robert Kizindo (Immunomodulation and Vaccines Programme, Medical Research Council/ Uganda Virus Research Institute and London School of Hygiene and Tropical Medicine Uganda Research Unit, Entebbe, Uganda)

Gloria Oduru (Immunomodulation and Vaccines Programme, Medical Research Council/ Uganda Virus Research Institute and London School of Hygiene and Tropical Medicine Uganda Research Unit, Entebbe, Uganda)

Prossy Kabuubi Nakawungu (Immunomodulation and Vaccines Programme, Medical Research Council/ Uganda Virus Research Institute and London School of Hygiene and Tropical Medicine Uganda Research Unit, Entebbe, Uganda)

Emmanuel Niwagaba (Immunomodulation and Vaccines Programme, Medical Research Council/ Uganda Virus Research Institute and London School of Hygiene and Tropical Medicine Uganda Research Unit, Entebbe, Uganda)

Elson Abayo (Entebbe Hospital, Wakiso District Local Government, Entebbe, Uganda)

Joyce Kabagenyi (Immunomodulation and Vaccines Programme, Medical Research Council/ Uganda Virus Research Institute and London School of Hygiene and Tropical Medicine Uganda Research Unit, Entebbe, Uganda)

Christopher Zziwa (Immunomodulation and Vaccines Programme, Medical Research Council/ Uganda Virus Research Institute and London School of Hygiene and Tropical Medicine Uganda Research Unit, Entebbe, Uganda)

Josephine Tumusiime (Entebbe Hospital, Wakiso District Local Government, Entebbe, Uganda)

Esther Nakazibwe (Entebbe Hospital, Wakiso District Local Government, Entebbe, Uganda)

James Kaweesa (Vector Control Division, Ministry of Health, Kampala, Uganda)
Fred Muwonge Kakooza (Koome Health Centre III, Mukono District Local Government, Mukono, Uganda)

Mirriam Akello (Immunomodulation and Vaccines Programme, Medical Research Council/ Uganda Virus Research Institute and London School of Hygiene and Tropical Medicine Uganda Research Unit, Entebbe, Uganda)

Lawrence Lubyayi (Immunomodulation and Vaccines Programme, Medical Research Council/ Uganda Virus Research Institute and London School of Hygiene and Tropical Medicine Uganda Research Unit, Entebbe, Uganda)

Jaco Verweij (Laboratory for Medical Microbiology and Immunology, St Elisabeth Hospital, Tilburg, the Netherlands)

Stephen Nash (MRC Tropical Epidemiology Group, Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, United Kingdom)

Ronald van Ree (Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands)

Harriet Mpairwe (Immunomodulation and Vaccines Programme, Medical Research Council/ Uganda Virus Research Institute and London School of Hygiene and Tropical Medicine Uganda Research Unit, Entebbe, Uganda)

Edridah Tukahebwa (Vector Control Division, Ministry of Health, Kampala, Uganda)

Emily L Webb (MRC Tropical Epidemiology Group, Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, United Kingdom)

Alison M Elliott (Immunomodulation and Vaccines Programme, Medical Research Council/ Uganda Virus Research Institute and London School of Hygiene and Tropical Medicine Uganda Research Unit, Entebbe, Uganda; Department of Clinical Research, London School of Hygiene and Tropical Medicine, London, United Kingdom)
for the LaVIISWA trial team

*These authors contributed equally

†Correspondence: Richard E Sanya, Immunomodulation and Vaccines Programme, Medical Research Council/ Uganda Virus Research Institute and London School of Hygiene and Tropical Medicine Uganda Research Unit, Entebbe, Uganda; Richard.Sanya@mrcuganda.org

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 hepatosplenomegaly 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 households.
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 ≥1 dose 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
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”.

[34] Variety of helminths, both gastrointestinal and blood flukes, cause considerable human morbidity and mortality. They are transmitted by snails and worms, and spread via the water supply. Schistosomiasis, for example, affects over 200 million people in sub-Saharan Africa, where it is endemic. The disease is caused by several species of Schistosoma, which are transmitted to humans by the Oncomelania snail. The snail is a vector of the biliary and intestinal forms of the disease, while the cercariae, which are released into the water, penetrate the skin of humans who come into contact with infected water. The cercariae are then transformed into schistosome adults in the small intestine or liver, respectively. The eggs are then excreted in the faeces and pass into the water, where they hatch into miracidia that infect the snail, completing the cycle. The disease can be prevented by improving water supply and sanitation, reducing contact with infected water, and using personal protective measures such as wearing shoes when walking in areas where schistosomiasis is prevalent. The disease is also treatable with praziquantel, a drug that kills the schistosome adults in the gut, but the treatment is not effective against the adult worms in the liver, which are the most serious form of the disease. This shortcoming has led to the development of new drugs, such as oxbendazole and mebendazole, which are effective against the adult worms in the liver, as well as the use of vaccines that are currently under development. These interventions have been shown to be effective in reducing the prevalence of schistosomiasis in endemic areas, but more research is needed to understand the long-term effects of these interventions on the health of the population. The disease is also associated with an increased risk of developing other diseases, such as hepatocellular carcinoma and bladder cancer, which can be prevented by the use of vaccines and chemotherapeutic agents. The prevalence of schistosomiasis is estimated to be as high as 76%, with more than 100 million people infected. The disease is more prevalent in children, with a prevalence of 90% in children under 15 years of age. The disease is more prevalent in males, with a prevalence of 84% in males and 45% in females. The disease is also more prevalent in rural areas, with a prevalence of 90% in rural areas and 2% in urban areas. The disease is also more prevalent in areas with poor sanitation, with a prevalence of 90% in areas with poor sanitation and 5% in areas with good sanitation. The disease is also more prevalent in areas with poor water supply, with a prevalence of 90% in areas with poor water supply and 5% in areas with good water supply. 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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**

Dr. van Ree reports personal fees from HAL Allergy BV, personal fees from Citeq BV, personal fees from ThermoFisher Scientific, outside the submitted work. All the other authors declare that they have no conflicts of interest.
REFERENCES


LaVIISWA trial team

Table 1. Characteristics of outcome survey participants

<table>
<thead>
<tr>
<th>Cluster-level characteristics</th>
<th>Standard arm (n=13)</th>
<th>Intensive arm (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean no. of households per village (range)</td>
<td>307 (124-882)</td>
<td>289 (87-544)</td>
</tr>
<tr>
<td>Mean no. of participating households (range)</td>
<td>55 (48-63)</td>
<td>54 (48-64)</td>
</tr>
<tr>
<td>Mean no. of individuals resident in participating households (range)</td>
<td>137 (89-161)</td>
<td>137 (85-177)</td>
</tr>
<tr>
<td>Mean no. of individuals included in analysis (range)</td>
<td>129 (84-150)</td>
<td>129 (79-169)</td>
</tr>
</tbody>
</table>

| 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% |

<table>
<thead>
<tr>
<th>Household-level characteristics</th>
<th>Standard arm (n=714)</th>
<th>Intensive arm (n=705)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median no. of household members (IQR)</td>
<td>2 (1-3)</td>
<td>2 (1-3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Individual-level characteristics</th>
<th>Standard arm (n=1675)</th>
<th>Intensive arm (n=1675)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, male</td>
<td>881 53%</td>
<td>857 51%</td>
</tr>
</tbody>
</table>

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)
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%

<table>
<thead>
<tr>
<th>Individuals aged 13 years and over</th>
<th>(n=1176)</th>
<th>(n=1112)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Frequency of lake contact (mv 9, 19)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Every day</td>
<td>911</td>
<td>776</td>
</tr>
<tr>
<td>Almost every day</td>
<td>126</td>
<td>147</td>
</tr>
<tr>
<td>Once a week</td>
<td>95</td>
<td>124</td>
</tr>
<tr>
<td>Once a month</td>
<td>30</td>
<td>35</td>
</tr>
<tr>
<td>Less than once a month</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>Never</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Individuals aged 18 years and over</th>
<th>(n=1116)</th>
<th>(n=1041)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV+ (mv 173, 176)</td>
<td>192</td>
<td>198</td>
</tr>
<tr>
<td>HIV+ on ART</td>
<td>90</td>
<td>103</td>
</tr>
<tr>
<td>HIV+ not on ART</td>
<td>93</td>
<td>90</td>
</tr>
<tr>
<td>HIV+ not known if receiving ART</td>
<td>9</td>
<td>5</td>
</tr>
</tbody>
</table>

*Figures in parentheses indicate missing values in the standard and intensive arm, respectively*
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Standard</th>
<th>Intensive</th>
<th>Unadjusted RR/GMR (95% CI)</th>
<th>p-value</th>
<th>Adjusted for outcome at baseline, age and sex RR/GMR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wheeze (age ≥ 5 years)</td>
<td>44/1384 (3.2%)</td>
<td>43/1392 (3.1%)</td>
<td>1.06 (0.61, 1.87)</td>
<td>0.82</td>
<td>1.11 (0.64, 1.93)</td>
<td>0.69</td>
</tr>
<tr>
<td>Wheeze (age &lt; 5 years)</td>
<td>6/284 (2.1%)</td>
<td>3/264 (1.1%)</td>
<td>1.00 (0.57, 1.80)</td>
<td>1.00</td>
<td>1.00 (0.57, 1.80)</td>
<td>1.00</td>
</tr>
<tr>
<td>Atopy (SPT)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPT positivity to any allergen</td>
<td>273/1514 (18.0%)</td>
<td>303/1523 (19.9%)</td>
<td>1.09 (0.83, 1.44)</td>
<td>0.51</td>
<td>1.10 (0.85, 1.42)</td>
<td>0.46</td>
</tr>
<tr>
<td>SPT positivity to <em>Dermatophagoides</em></td>
<td>162/1514 (10.7%)</td>
<td>164/1523 (10.8%)</td>
<td>0.98 (0.72, 1.35)</td>
<td>0.92</td>
<td>1.00 (0.74, 1.36)</td>
<td>0.99</td>
</tr>
<tr>
<td>SPT positivity to <em>Blomia tropicalis</em></td>
<td>102/1514 (6.7%)</td>
<td>127/1522 (8.3%)</td>
<td>1.26 (0.83, 1.90)</td>
<td>0.26</td>
<td>1.27 (0.85, 1.91)</td>
<td>0.22</td>
</tr>
<tr>
<td>SPT positivity to German cockroach</td>
<td>156/1513 (10.3%)</td>
<td>194/1522 (12.8%)</td>
<td>1.24 (0.87, 1.77)</td>
<td>0.20</td>
<td>1.22 (0.87, 1.71)</td>
<td>0.21</td>
</tr>
<tr>
<td>Atopy (IgE detected by ImmunoCAP)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Dermatophagoides</em> or cockroach positivity</td>
<td>214/390 (54.9%)</td>
<td>210/390 (53.9%)</td>
<td>0.97 (0.83, 1.13)</td>
<td>0.67</td>
<td>0.96 (0.82, 1.12)</td>
<td>0.60</td>
</tr>
<tr>
<td>(&gt;0.35kUa/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Dermatophagoides</em> positivity (aslgE&gt;0.35kUa/L)</td>
<td>134/390 (34.4%)</td>
<td>130/390 (33.3%)</td>
<td>0.95 (0.76, 1.20)</td>
<td>0.67</td>
<td>0.96 (0.77, 1.19)</td>
<td>0.68</td>
</tr>
<tr>
<td>German cockroach positivity (aslgE&gt;0.35kUa/L)</td>
<td>201/390 (51.5%)</td>
<td>192/390 (49.2%)</td>
<td>0.94 (0.80, 1.11)</td>
<td>0.47</td>
<td>0.94 (0.79, 1.11)</td>
<td>0.42</td>
</tr>
</tbody>
</table>
Concentration of asIgE to *Dermatophagoides* (kUa/L)<sup>c</sup>  
<table>
<thead>
<tr>
<th></th>
<th>GM: 0.158</th>
<th>GM: 0.129</th>
<th>0.78 (0.51, 1.17)</th>
<th>0.22</th>
<th>0.77 (0.52, 1.13)</th>
<th>0.17</th>
</tr>
</thead>
</table>

Concentration of asIgE to German cockroach (kUa/L)<sup>c</sup>  
|          | 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*<sup>d</sup>  
|          | 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<sup>d</sup>  
|          | GM: 72.4  | GM: 161.0 | 1.98 (0.59, 6.63) | 0.25 | 1.51 (0.45, 5.04) | 0.49 |

by IgE were adjusted for age and sex only; <sup>b</sup>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; <sup>c</sup>log10(+0.001) transformation at individual level; <sup>d</sup>log10(+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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>n/N (%) / arithmetic mean</th>
<th>Unadjusted</th>
<th>Adjusted for outcome at baseline, age and sex</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Standard</td>
<td>Intensive</td>
<td>RR/mean difference (95% CI)</td>
</tr>
<tr>
<td>Helminth infections</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schistosoma mansoni, stool Kato Katz</td>
<td>523/1355 (38.6%)</td>
<td>323/1396 (23.1%)</td>
<td>0.64 (0.43, 0.94)</td>
</tr>
<tr>
<td>Schistosoma mansoni, stool PCR</td>
<td>797/1353 (59.9%)</td>
<td>541/1394 (38.8%)</td>
<td>0.68 (0.52, 0.89)</td>
</tr>
<tr>
<td>Schistosoma mansoni, urine CCA</td>
<td>1229/1444 (85.1%)</td>
<td>1216/1435 (84.7%)</td>
<td>0.99 (0.91, 1.08)</td>
</tr>
<tr>
<td>Hookworm, stool PCR&lt;sup&gt;a&lt;/sup&gt;</td>
<td>147/1353 (10.9%)</td>
<td>112/1394 (8.0%)</td>
<td>0.54 (0.28, 1.02)</td>
</tr>
<tr>
<td>Strongyloides stercoralis, stool PCR</td>
<td>112/1353 (8.3%)</td>
<td>78/1394 (5.6%)</td>
<td>0.74 (0.50, 1.11)</td>
</tr>
<tr>
<td>Trichuris trichiura, stool Kato Katz</td>
<td>137/1355 (10.1%)</td>
<td>108/1396 (7.7%)</td>
<td>0.91 (0.40, 2.09)</td>
</tr>
<tr>
<td>Ascaris lumbricoides, stool Kato Katz</td>
<td>11/1355 (0.8%)</td>
<td>3/1396 (0.2%)</td>
<td></td>
</tr>
<tr>
<td>Clinical outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visible flexural dermatitis</td>
<td>1/1558 (0.1%)</td>
<td>4/1553 (0.3%)</td>
<td></td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>14.0</td>
<td>13.9</td>
<td>-0.06 (-0.37, 0.25)</td>
</tr>
</tbody>
</table>
### Anthropometry

<table>
<thead>
<tr>
<th>Measure</th>
<th>Mean</th>
<th>95% CI</th>
<th>p-value</th>
<th>99% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height-for-age z-score, age 1-19 years</td>
<td>-0.48</td>
<td>-0.49</td>
<td>0.95</td>
<td>0.02</td>
<td>0.83</td>
</tr>
<tr>
<td>Weight-for-age z-score, age 1-10 years</td>
<td>-0.06</td>
<td>-0.17</td>
<td>0.27</td>
<td>-0.05</td>
<td>0.52</td>
</tr>
<tr>
<td>Weight-for-height z-score, age 1-5 years</td>
<td>0.15</td>
<td>0.19</td>
<td>0.62</td>
<td>-0.06</td>
<td>0.72</td>
</tr>
</tbody>
</table>

### Hepatosplenomegaly, palpation

<table>
<thead>
<tr>
<th>Measure</th>
<th>Villages</th>
<th>%</th>
<th>95% CI</th>
<th>p-value</th>
<th>99% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatomegaly, palpation</td>
<td>100/1546</td>
<td>6.5%</td>
<td>0.97 (0.71, 1.32)</td>
<td>0.83</td>
<td>0.96 (0.70, 1.32)</td>
<td>0.80</td>
</tr>
<tr>
<td>Splenomegaly, palpation</td>
<td>87/1549</td>
<td>5.6%</td>
<td>0.73 (0.43, 1.25)</td>
<td>0.20</td>
<td>0.70 (0.43, 1.15)</td>
<td>0.13</td>
</tr>
<tr>
<td>Hepatosplenomegaly, palpation¹</td>
<td>22/1548</td>
<td>1.4%</td>
<td>0.85 (0.52, 1.39)</td>
<td>0.49</td>
<td>0.78 (0.47, 1.30)</td>
<td>0.33</td>
</tr>
</tbody>
</table>

### Reported clinical outcomes (exploratory)

<table>
<thead>
<tr>
<th>Measure</th>
<th>Villages</th>
<th>%</th>
<th>95% CI</th>
<th>p-value</th>
<th>99% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urticaria, last 12 months</td>
<td>162/1667</td>
<td>9.7%</td>
<td>1.06 (0.86, 1.30)</td>
<td>0.59</td>
<td>1.06 (0.88, 1.27)</td>
<td>0.51</td>
</tr>
<tr>
<td>Rhinitis, last 12 months</td>
<td>78/1667</td>
<td>4.7%</td>
<td>1.02 (0.73, 1.42)</td>
<td>0.92</td>
<td>1.00 (0.74, 1.36)</td>
<td>0.99</td>
</tr>
</tbody>
</table>

¹For 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
Figure 2

26 villages
7741 eligible households

Standard intervention
13 villages
3900 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)

Households included (n=714)

Households excluded (n=196)

Households included (n=705)

Households excluded (n=205)

Reasons for household exclusion:
Empty house (n=46)
Occupants absent (n=78)
Refused (n=30)
Household demolished (n=10)
Other (n=11)
Consented, no demographics (n=7)

Reasons for household exclusion:
Empty house (n=40)
Occupants absent (n=81)
Refused (n=6)
Household demolished (n=20)
Other (n=9)
Consented, no demographics (n=10)

Individual participants (n=1796)
Interviewed (n=1667)
Not interviewed (n=119)

Individual participants (n=1798)
Interviewed (n=1666)
Not interviewed (n=124)

Reasons not interviewed:
Absent for work (n=89)
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=1676; 98.9%)
Any SPT (n=1571; 90.4%)
IgE ELISA (n=1475; 88.1%)
IgE ImmunoCAP (n=390; 23.3%)

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