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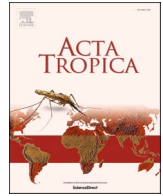
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Individual-level analysis of the efficacy of albendazole and albendazole-ivermectin fixed-dose coformulation (FDC) against *Trichuris trichiura* and hookworms

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ABSTRACT

Background: Anthelmintic drugs are vital for controlling soil-transmitted helminths (STH), but treatment failures remain common. The egg reduction rate (ERR) is a key metric for assessing anthelmintic efficacy. This study calculated individual ERRs (ERRi) to evaluate a new anthelmintic drug and identify factors associated with treatment failure.

Methodology: Data were collected from 369 children infected with *T. trichiura* and 226 infected with hookworms, who participated in a Phase II/III clinical trial. Participants received a single dose of ivermectin/albendazole 9/400 mg or 18/400 mg fixed-dose coformulation (FDC) or albendazole 400 mg (ALB). Egg counts were measured pre- and post-treatment using the Kato-Katz test. A Bayesian mixed model was used to calculate ERRi and assess covariates influencing treatment response.

Results: In *T. trichiura*-infected participants ($n = 369$), complete therapeutic failure (uncured and lacking significant ERRi) occurred in 54 % of the albendazole group compared to 7 % in the FDC group. Notably, 59 % of uncured participants in the FDC arm achieved significant ERRi, versus only 16 % in the albendazole arm. Co-infections influenced outcomes: *A. lumbricoides* co-infection improved response in the albendazole group, while *S. stercoralis* co-infection reduced efficacy in the FDC arm. Among hookworm-infected participants ($n = 226$), complete failure was observed in 15 % (albendazole) and 10 % (FDC). Both arms showed 56 % of uncured participants achieving significant ERRi. *S. stercoralis* co-infection was linked to poorer response in the FDC arm, while no covariates influenced albendazole response. ERRi modeling demonstrated the superior efficacy of FDC over albendazole in *T. trichiura* treatment, with comparable efficacy for hookworms.

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1. Introduction

Soil-transmitted helminths (STH) are a group of parasitic worms that includes *Ascaris lumbricoides*, *Trichuris trichiura* (*T. trichiura*) and hookworms (*Ancylostoma duodenale* and *Necator americanus*); and infect >1.5 billion people worldwide (World Health Organization, 2023). The recommended treatment for STH in endemic areas is preventive chemotherapy with a single dose of mebendazole or albendazole in pre-school and school-aged children, and women of childbearing age (World Health Organization, 2020). These drugs exhibit high efficacy against *A. lumbricoides*, moderate efficacy against hookworms, and low efficacy against *T. trichiura* (Moser et al., 2017). In recent years, there has been a growing focus on combination chemotherapies as a strategic approach to control STH infections, aiming to enhance efficacy while mitigating the risk of emergence of drug resistance. The most promising drugs being emodepside and the oxantel pamoate/albendazole and albendazole/ivermectin combinations (Welsche et al., 2023, Speich et al., 2012, Sprecher et al., 2023, Speich et al., 2014, Mrimi et al., 2023, Speich et al., 2015). However, oxantel/albendazole pamoate has low efficacy against *A. lumbricoides* and hookworms and Emodepside is in the experimental phase for use in humans, so the combination of albendazole/ivermectin remains the preferred choice (Keiser, 2023). The co-administration of albendazole and ivermectin has been used for years, but has the limitation that the recommended dose of ivermectin is weight-adjusted and may include the intake of several tablets, hence resulting challenging, mainly considering its use in children. To overcome this limitation, we developed and tested a fixed-dose coformulation of ivermectin/albendazole (FDC) 9/400 mg (to use below 45 kg body-weight) and 18/400 mg (to use above 45 kg body-weight) orodispersible tablets (Krolewiecki et al., 2022). As overall findings, a single dose FDC demonstrated superior efficacy to the standard albendazole 400 mg for the treatment of *T. trichiura* and satisfactory efficacy for the treatment of hookworms, whereas showing a similar safety profile (Krolewiecki et al., 2025).

In clinical trials, the efficacy of drugs for the treatment of STH is measured at the population level by the cure rate (CR), defined as the percentage of participants cured after treatment, or the egg reduction rate (ERR), defined as, one minus the ratio of the mean of the egg counts after and before treatment (Moser et al., 2020). While CR and ERR are suitable for comparing drug efficacy at the population level, they do not take into account individual variability in response to treatment, which makes interpretation at the individual level difficult. The model-based approach is a tool that allows the use of individual patient data to assess treatment response at the individual level. Models such as mixed models with a Bayesian approach have been successfully applied for the assessment of variation among similar individuals sharing covariates, letting the estimation of individual egg reduction rates (ERRI) while simultaneously assessing the impact of covariates (Walker et al., 2014, Crellen et al., 2016, Walker et al., 2016, Walker et al., 2021). This approach provides a better understanding of the efficacy of anthelmintics because allow the identification of covariables that are associated with therapeutic failures. These models also help to detect changes in treatment response among individuals that may indicate a decreased response to treatment (Walker et al., 2014).

In this study, we analyzed data from a clinical trial to model the ERRI of FDC and albendazole in participants infected with *T. trichiura* and hookworms across Ethiopia, Kenya, and Mozambique. Additionally, we evaluated the covariables that can contribute to therapeutic failure.

2. Methods

2.1. Data and study population

The data for this study were obtained from an adaptive Phase II/III, single-blinded (outcome assessor-blinded), randomized, multicenter, parallel-group, active-controlled, superiority clinical trial conducted in

Kwale County (Kenya, Bahir Dar Zuria (Ethiopia, and Manhiça District (Mozambique) (Krolewiecki et al., 2022).

Safety and the efficacy of the FDC of ALB 400 mg and IVM at either 9 mg or 18 mg against *T. trichiura* and hookworms were evaluated. FDC was evaluated at single-dose or three consecutive daily doses, in comparison with ALB 400 mg single dose (control group) (Krolewiecki et al., 2022). For each participant, a single stool sample was collected at baseline and 21 ± 7 days after treatment and egg counts were performed by double Kato-Katz for the three STH species, while a modified Baermann was done for the detection of *S. stercoralis* larvae (Krolewiecki et al., 2022). The Kato-Katz technique consists of preparing standardized thick smears of stool using a 41.7 mg template to quantify eggs per gram of stool (EPG). In contrast, the modified Baermann method is an incubation-based technique in which stool is mixed with charcoal, wrapped in gauze, and suspended in warm water to facilitate the active migration of Strongyloides stercoralis larvae from the sample. All stools were processed within 24 h of collection, and Kato-Katz smears were examined within 30 min of preparation to optimize the detection of fragile hookworm eggs. In addition, qPCR was performed for the detection of the three STH and *S. stercoralis* in stool samples before and after treatment, but these results will be published in the future. A participant was considered cured if the egg count was zero 21 ± 7 days after treatment, while the participant was classified as not cured if eggs were still present. The primary efficacy outcome was the cure rate, defined as the proportion of cured participants out of the total, and the secondary outcome was ERR, calculated as one minus the ratio of the mean post-treatment egg count to the mean pre-treatment egg count.

This study included only participants who received a single dose of either albendazole or FDC. The results of the FDC treatment arm administered over three consecutive days were not modeled due to the limited number of therapeutic failures observed in that arm. The description of the baseline characteristics and efficacy results of the intention-to-treat population of the clinical trial have been reported elsewhere (Krolewiecki et al., 2025).

The population used in this study comprises two populations from the clinical trial defined as:

- *T. trichiura* infected population: randomized participants, not withdrawn, infected with *T. trichiura* at baseline in Kenya and Mozambique who had microscopy data at baseline and at 21 days after treatment. Participants from Ethiopia were not included due to insufficient numbers ($n = 1$) to be analyzed.
- Hookworm infected population: randomized participants, not withdrawn, infected with hookworms at baseline in Kenya and Ethiopia who had microscopy data at baseline and 21 days after treatment. Participants from Mozambique were not included due to insufficient numbers ($n = 3$) to be analyzed.

2.2. Statistical analysis

To calculate body composition, body mass index (BMI) was used as an indicator, and values were interpreted using the age and sex growth curves developed by the Centers for Disease Control and Prevention, which provide specific percentiles to classify body composition status according to the age and sex of the child. The participants were classified as underweight: BMI below the 5th percentile, Healthy weight: BMI between the 5th and 85th percentiles, Overweight: BMI between the 85th and 95th percentiles, and Obesity: BMI at or above the 95th percentile. These calculations were performed using the PAutilities library of R software (Hibbing, 2019, R Core Team 2021).

For participants who received FDC, the dose of IVM received was calculated in $\mu\text{g/kg}$, and they were categorized into three categories: $\text{dose} < 300 \mu\text{g/kg}$, $300 \mu\text{g/kg} \leq \text{dose} < 400 \mu\text{g/kg}$, and $\text{dose} \geq 400 \mu\text{g/kg}$. These ranges were chosen based on the median and inter-quartile range of the ivermectin dose of all participants.

The cure rate and its 95 % confidence interval were calculated using

a binomial distribution, whereas the ERR based on the arithmetic mean and its 95 % confidence interval were estimated using Bootstrap resampling method.

To model the ERRi we use a mixed model fitted in a Bayesian framework previously described by other authors (Walker et al., 2014, Crellen et al., 2016, Walker et al., 2016). This model allows inferences to be made at the individual level by explicitly modelling the conditional dependence of the data using fixed and random effects (Walker et al., 2016). The model is a log-linear regression framework to elucidate the alteration in egg counts after treatment ($x = 1$) in comparison to before treatment ($x = 0$), employing a multiplicative approach. Covariates are integrated into the regression structure through interaction with x , enabling ERR variations across strata via fixed effects and further among individuals through random effects (Crellen et al., 2016, Walker et al., 2016). The fixed effects were study site (country), co-infections with other STH species, body composition, sex, age range, and dose of ivermectin (only in those who received FDC and were infected with *T. trichiura*), while the random effect was the Participant identification. Separate models were fitted for each treatment arm and for *T. trichiura* and hookworms. For each model, three Markov chain Monte Carlo simulations were run using the MCMCglmm library (Hadfield, 2010), and convergence was verified using the Gelman-Rubin statistic for each variable with the coda library (Plummer et al., 2006). In each simulation, non-informative prior distributions were used and Markov chains were run for 1000,000 iterations with a burn-in of 2500 iterations.

In the context of the generalized linear mixed model, an "average participant" is defined as a hypothetical individual whose fixed-effect covariates are set to their reference levels (e.g., Sex=male, Site=Kenya, Body composition= Healthy weight), and whose individual-level random effects are centered at zero. This represents the

average population-level effects without additional variation introduced by individual deviations.

The model coefficients (MC) for each covariate indicate the multiplicative change in egg counts measured after treatment in an average participant in a particular covariate group compared to egg counts measured after treatment in an average participant in the reference group (Walker et al., 2016). A coefficient was considered statistically different from zero when its associated p-value was <0.05 . Negative coefficients in the time-covariate interaction indicate higher ERRi and the inverse for positive coefficients. For each coefficient, the posterior means and 95 % credible intervals (95 % CrI), defined as the interval that has a 95 % probability of containing the true value, was calculated. For each participant and each covariate group, the posterior mean of ERRi with its 95 % CrI was calculated. For a participant the ERRi was considered significant when the 95 % CrI did not contain zero. Complete therapeutic failure was considered when a participant was categorized as not cured and presented a non-significant ERRi. In an average participant for a given covariate, if the credible interval includes zero, it indicates uncertainty in the estimate, meaning that neither a reduction nor an increase in egg counts after treatment can be ruled out, and it remains possible that the ERRi is not meaningfully different from zero.

The R code to fit the models has already been published (Walker et al., 2014, Crellen et al., 2016). All analyses were performed with R software version 4.1.2 (R Core Team 2021).

3. Results

3.1. Characteristics of study populations

The populations for *T. trichiura* and hookworms included 369 and

Table 1

Baseline characteristics of participants and efficacy of treatment arms. FDC: fixed-dose coformulation of ivermectin/albendazole.

	<i>T. trichiura</i> infected population (n = 369)		Hookworm infected population (n = 226)	
	Albendazole (n = 123)	FDC (n = 246)	Albendazole (n = 102)	FDC (n = 124)
Site (n, % by site)				
Ethiopia	–	–	87 (85 %)	95 (77 %)
Kenya	92 (75 %)	183 (74 %)	15 (15 %)	29 (23 %)
Mozambique	31 (25 %)	63 (26 %)	–	–
Biological sex (n, % by sex)				
Male	65 (53 %)	122 (50 %)	57 (56 %)	70 (56 %)
Female	58 (47 %)	124 (50 %)	45 (44 %)	54 (44 %)
Age (Median – Interquartile range)				
11 (8, 13)		10 (8, 12)	12 (10, 14)	11 (10, 14)
Body composition (n, % by strata)				
Underweight	58 (47 %)	107 (43 %)	61 (60 %)	61 (49 %)
Healthy Weight	62 (50 %)	136 (55 %)	40 (39 %)	63 (51 %)
Overweight	2 (2 %)	2 (1 %)	0 (0 %)	0 (0 %)
Obese	1 (1 %)	0 (0 %)	1 (1 %)	0 (0 %)
Severe obese	0 (0 %)	1 (0 %)	0 (0 %)	0 (0 %)
Participants with Related Adverse Events – Gastrointestinal Disorders (n, %)	20 (16 %)	56 (23 %)	9 (9 %)	10 (8 %)
Ivermectin dose (n, % by dose)				
200µg/Kg ≤ Dose < 300µg/kg	–	66 (27 %)	–	45 (36 %)
300µg/kg ≤ Dose < 400 µg/kg	–	100 (41 %)	–	56 (45 %)
≥ 400 µg/kg	–	100 (33 %)	–	56 (19 %)
Infection intensity				
Median EPG (Interquartile range)	108 (48, 264)	108 (48, 312)	120 (36,252)	120 (60,270)
Light (n, %)	113 (92 %)	224 (91 %)	100 (98 %)	121 (98 %)
Moderate and heavy (n, %)	10 (8 %)	22 (9 %)	2 (2 %)	3 (2 %)
Co-infections (n, %)				
Co-infection with <i>A. lumbricoides</i>	15 (12 %)	21 (9 %)	0 (0 %)	0 (0 %)
Co-infection with hookworms	3 (2 %)	19 (8 %)	–	–
Co-infection with <i>S. stercoralis</i>	1 (1 %)	9 (4 %)	8 (8 %)	17 (14 %)
Co-infection with <i>T. trichiura</i>	–	–	3 (3 %)	18 (15 %)
Efficacy				
Cured participants (n)	44	207	68	97
Not cured participants (n)	79	39	34	27
Cure rate (CI 95 %)	35.8 (27.5,45.0)	84.1 (78.8,88.4)	66.7 (56.6,75.6)	78.2 (69.7,84.9)
Egg reduction rate (arithmetic mean, CI 95 %)	40.8 (–3.8,56.6)	96.4 (94.4,98.0)	91.6 (73.7,96.8)	94.5 (88.1,97.4)

226 participants respectively (Table 1). Most of the participants infected with *T. trichiura* were from Kenya, while most of the participants infected with hookworms were from Ethiopia. In addition, it was observed that most of the participants infected with hookworms were older than ten years. Most of the infections were of light intensity. Regarding body composition, it was observed that approximately half of the participants were underweight, and very few were overweight or obese ($n = 9$). Among participants infected with *T. trichiura* the most common co-infection was with *A. lumbricoides* while for participants infected with hookworms it was co-infection with *S. stercoralis*. The efficacy results for both populations are similar to those published for the intent-to-treat (ITT) population (Krolewiecki et al., 2025). All the participants who received FDC received doses greater than 200 $\mu\text{g}/\text{kg}$. The most frequent adverse events were gastrointestinal disorders.

3.2. Individual-level efficacy of albendazole and FDC in *T. trichiura* infection

Among the participants infected with *T. trichiura*, it was observed that 54 % (66/123) in the albendazole arm and 7 % (16/246) in the FDC

arm presented complete therapeutic failure (Fig. 1). Furthermore, when looking at the not cured participants, it was observed that in the albendazole arm only 16 % (13/79) significantly reduced egg counts, while in the FDC arm, 59 % (23/39) of the not cured participants significantly reduced egg counts (Fig. 1).

In reference to the covariates assessed in the models, co-infections were found to affect the efficacy of albendazole and FDC in *T. trichiura*-infected participants. In the albendazole arm, we observed that an average participant co-infected with *A. lumbricoides* had a better response to treatment (MC: -2.2 (95 % CrI: $-4.3, -0.3$) $p = 0.022$) (Fig. 2A), and an average co-infected participant with *A. lumbricoides* showed a higher ERRi (65.0 (95 % CrI: 30.7,83.7)) than without co-infection (mean ERRi: -44.1 (95 % CrI: $-132.6,3.2$)) (Fig. 2B). In FDC-treated participants, there were no differences between *A. lumbricoides* co-infected and non-co-infected participants. It was also observed that a participant co-infected with *S. stercoralis* showed a worse response to treatment with FDC (MC: 3.2 (95 % CrI: 2.2, 6.4) $p = 0.026$). A lower mean ERRi in an average participant co-infected with *S. stercoralis* (mean ERRi: 14.2 (95 % CrI: $-200.8,83.2$)), compared to an average participant non-co-infected (mean ERRi: 94.7 (95 % CrI:

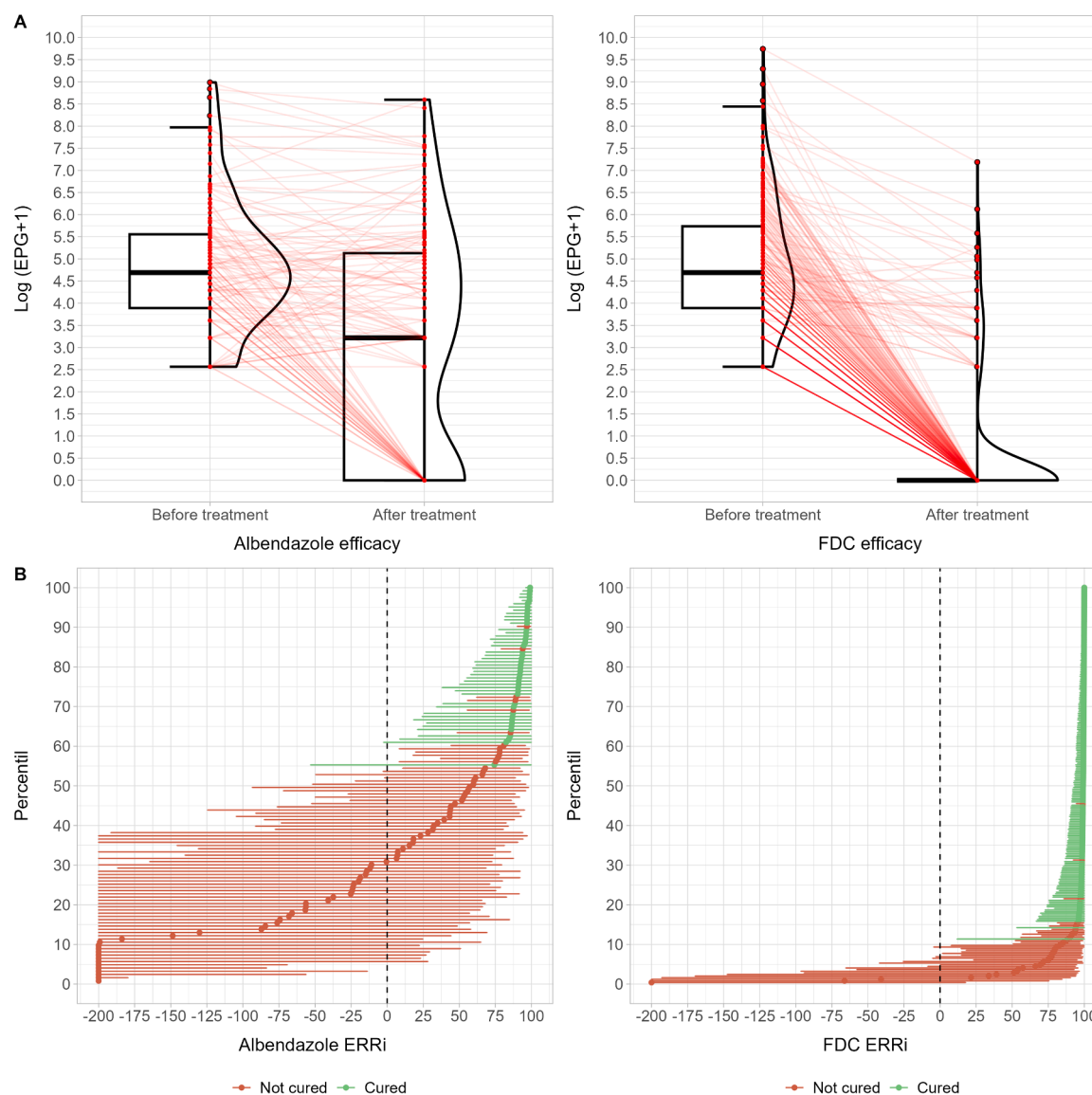


Fig. 1. Estimated ERRi of albendazole and FDC in participants infected with *T. trichiura*. A. Variation of eggs per gram (EPG) in stool by Kato-Katz before and after treatments. B. Posterior mean (red dot) with its 95 % credible confidence interval (green line for cured participants and red line for not cured participants) of the ERRi of each participant. On the left are the results for albendazole and on the right for FDC: Fixed-Dose Coformulation ivermectin/albendazole.

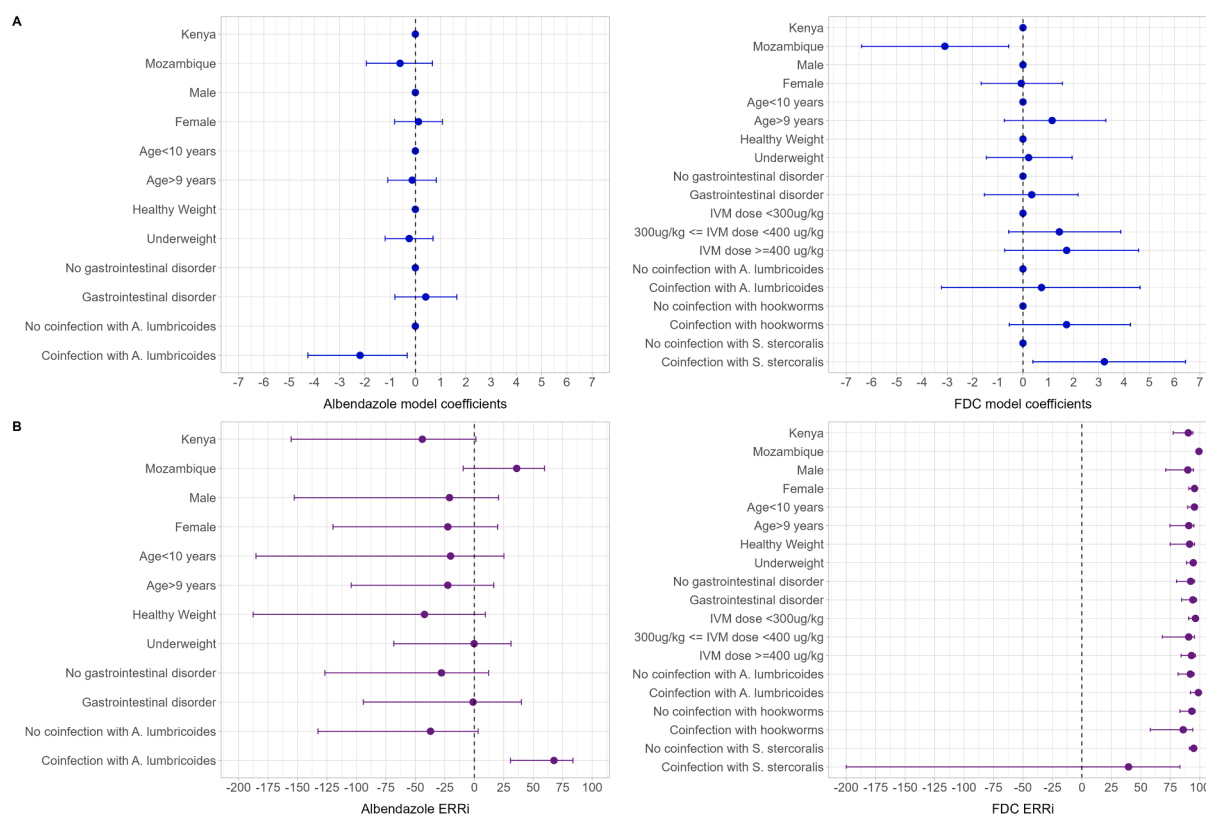


Fig. 2. Impact of covariates coefficients on the efficacy of albendazole and FDC in participants infected with *T. trichiura*. A. Posterior mean (blue dot) with its 95 % credible confidence interval (cyan line) of the fixed-effect coefficients estimated by the model. The reference category has zero value, significant coefficients do not contain zero in the credible confidence interval. Negative coefficient values indicate higher ERRi and vice versa. B. Posterior mean (violet dot) with its 95 % credible confidence interval (violet line) of the ERRi for an average participant in each category of each fixed effect. On the left are the results for albendazole and on the right for FDC: Fixed-Dose Coformulation ivermectin/albendazole.

91.2,96.7)) was observed (Fig. 2B). Co-infection with hookworms and *S. stercoralis* was not evaluated in the albendazole arm due to the low number of co-infected participants.

The country was also found to affect the efficacy of the FDC, as a better response FDC was observed in an average participant from Mozambique (mean ERRi: 99.1 (95 % CrI: 97.5,99.8)) compared to an average participant from Kenya (mean ERRi: 90.2 (95 % CrI: 81.0,94.5)) (MC: -3.1 (95 % CrI: $-6.8, -0.5$) $p = 0.017$) (Fig. 2B).

No associations between age, sex, body composition, intensity of infection and the occurrence of gastrointestinal adverse events with response to treatment were observed for any of the treatment arms. In the FDC arm, no association between ivermectin dose and treatment response was observed.

The coefficients estimated by the model (95 % CrI, p values and Gelman-Rubin statistic) for participants infected with *T. trichiura* and treated with albendazole or the FDC can be seen in supplementary materials (Table S1, and Table S2).

3.3. Individual-level efficacy of albendazole and FDC in hookworm infection

Among participants infected with hookworms, 15 % (15/102) of those treated with albendazole and 10 % (12/124) of those treated with FDC showed complete therapeutic failure (Fig. 3). In addition, among not cured participants, 56 % (albendazole 19/34, FDC 15/27) in both treatment arms significantly reduced egg counts.

In the albendazole arm, none of the evaluated covariates showed any significant association with treatment response (Fig. 4A). However, in the FDC arm, an average participant co-infected with *S. stercoralis* exhibited a poorer treatment response compared to an average

participant with single infection (MC: 2.4 (95 % CrI: 0.1, 5.2), $p = 0.036$) (Fig. 4A). Specifically, the ERRi was 63.9 (95 % CrI: 8.1, 87.1) among participants with *S. stercoralis* co-infection, contrasting with 87.7 (95 % CrI: 68.6, 94.7) among those with no co-infection (Fig. 4B).

The coefficients estimated by the models (95 % CrI, p values, and Gelman-Rubin statistic) for participants infected with hookworms and treated with albendazole and FDC can be seen in supplementary materials (Table S3 and Table S4).

4. Discussion

In this study we have expanded and complemented the efficacy results of a clinical trial, by focusing on the stool egg count-based effectiveness of albendazole and FDC at the individual level, analyzing the data using a Bayesian approach. Our findings confirmed the low efficacy of albendazole in treating *T. trichiura*, in contrast to the higher efficacy observed with FDC. Additionally, FDC demonstrated adequate efficacy for the treatment of hookworms.

The low efficacy of albendazole in treating *T. trichiura* infection has been demonstrated in several clinical trials with cure rates between 21 % and 42 %, and ERRs at population level between 39 % and 60 % (Moser et al., 2017). There is a tendency to believe that even if albendazole does not achieve cure it helps to reduce the parasite load, which is true at the population level, however, this does not seem to be true at the individual level. Studies using data from several clinical trials revealed that 28 % of the participants had an ERRi=0 (Olliaro et al., 2022), whereas in our study participants infected with *T. trichiura* and assigned to the albendazole arm, only 16 % of non-cured participants had significantly reduced egg counts after treatment. This suggests that there are two different populations of individuals and/or worms that

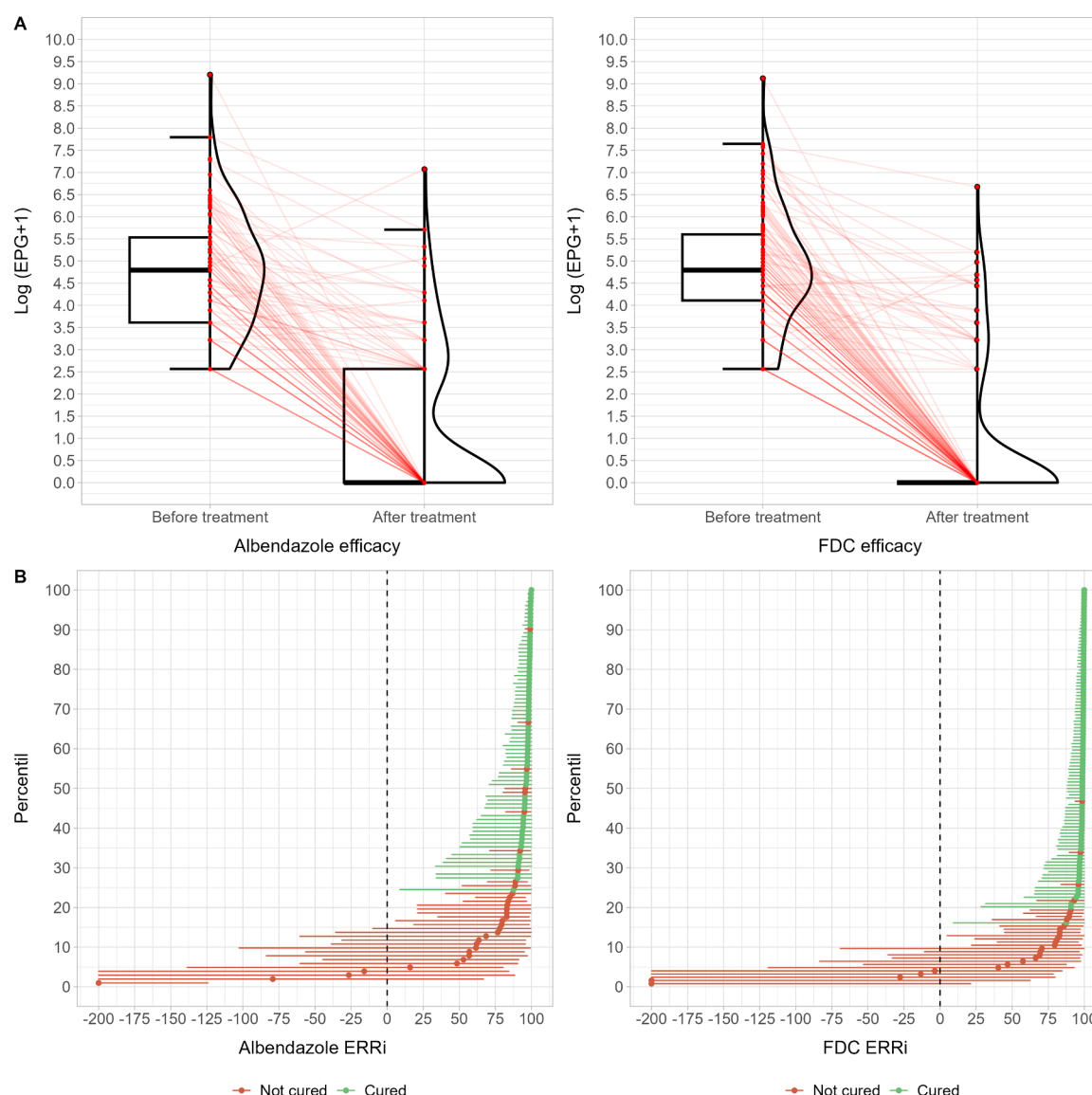


Fig. 3. Estimated ERRi of albendazole and FDC in participants infected with hookworms. A. Variation of eggs per gram (EPG) in stool by Kato-Katz before and after treatments. B. Posterior mean (red dot) with its 95 % credible confidence interval (green line for cured participants and red line for not cured participants) of the ERRi of each participant. On the right are the left for albendazole and on the right for FDC: Fixed-Dose Coformulation ivermectin/albendazole.

respond differently to the treatment: one population responsive to the treatment either by cure or egg count reduction, and other population that does not respond at all to albendazole, thus most of the treatment outcomes are complete therapeutic failures. To date, there is not yet a comprehensive explanation that describes the variability of albendazole efficacy between individuals. Among the leading hypotheses, one suggests that the pharmacokinetics of albendazole varies significantly between individuals infected with STH, potentially influencing the clearance of parasites post-treatment (Whittaker et al., 2022). However, higher doses of albendazole did not result in improved efficacy against *T. trichiura* (Patel et al., 2020). Another theory postulates that genetic factors within the parasite population may confer resistance to the drug, possibly exacerbated by exposure to prolonged mass drug administration with benzimidazoles (Moser et al., 2017). In our opinion, the second theory could better explain the presence of two different populations that respond differently to treatment as well as because participants that received FDC did show significant ERR after treatment when compared to albendazole.

It has been shown that the efficacy of albendazole and the albendazole/ivermectin combination for the treatment of *T. trichiura* can vary

between countries (Hürlimann et al., 2022). We observed that the posterior mean ERRi for both albendazole and FDC was higher in Mozambique than in Kenya. However, this difference was only significant for individuals treated with FDC. This difference may be due to different strains of parasite or to differences in Kato-Katz performance. For a better understanding of this, future analyses of the genetic diversity of the helminth eggs found, as well as qPCR analysis of the stool samples, will be carried out (Krolewiecki et al., 2022).

Another possible cause of the reduced efficacy of albendazole in infections with *T. trichiura* is co-infection with other STH (Kabatende et al., 2023). Co-infection between *T. trichiura* and *A. lumbricoides* is very common in areas where both are endemic and there is a scarce supply of potable water, but it is unclear whether these co-infections are a mere coincidence or if there is any interaction between them that could alter the infection in humans (Else et al., 2020; Echazú et al., 2015). We observed a better response to treatment in participants coinfecting with *A. lumbricoides*. Similar results were obtained in a clinical trial conducted in Ethiopia, Laos, and Pemba Island, in which the subsequent mean ERRi among participants coinfecting with *T. trichiura* and *A. lumbricoides* was higher than those with a single *T. trichiura* infection,

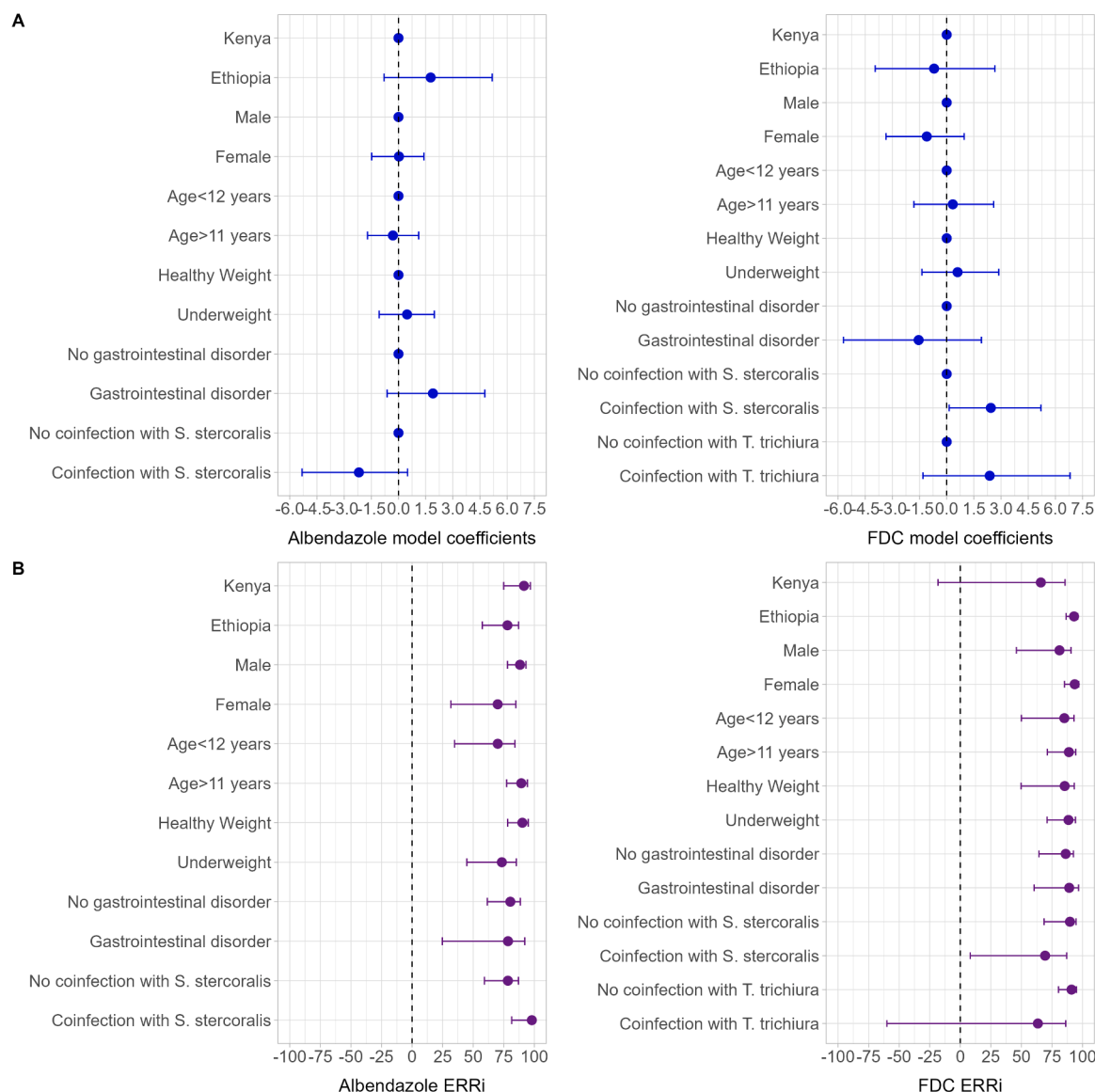


Fig. 4. Impact of covariates coefficients on the efficacy of albendazole and FDC in participants infected with hookworms. A. Mean (blue dot) with its 95 % credible confidence interval (cyan line) of the fixed-effect coefficients estimated by the model. The reference category has zero value, significant coefficients do not contain zero in the credible confidence interval. Negative coefficient values indicate higher ERRi and vice versa. B. Posterior mean (violet dot) with its 95 % credible confidence interval (violet line) of the ERRi for an average participant in each category of each fixed effect. On the left are the results for albendazole and on the right for FDC: Fixed-Dose Coformulation ivermectin/albendazole.

although this difference was not significant (Walker et al., 2021), whereas a study in Rwanda showed a lower ERR in participants coinfecting with STH (Kabatende et al., 2023). Based on these results, the association between *T. trichiura* and *A. lumbricoides* co-infection and treatment response remains unclear.

Despite the reduced efficacy of albendazole in participants infected with *T. trichiura*, albendazole showed satisfactory efficacy in participants infected with hookworms (World Health Organization, 2013). We used the standard 400 mg dose, but unlike *T. trichiura*, higher doses of albendazole have been shown to increase efficacy against hookworm, demonstrating that exposure of the parasite to the drug determines its efficacy (Patel et al., 2021). We observed complete therapeutic failure in only 15 % of the participants. These results are in agreement with other trials that observed a reduction in the prevalence of hookworm infection after massive administration of albendazole (Pion et al., 2020). Our results thus suggest that albendazole can still be a valuable option for the treatment and control of hookworm infection. Furthermore, our findings are in line with other studies that found no association between the

efficacy of albendazole against hookworms, and age, biological sex, body composition or co-infections with other STH (Colella et al., 2021, Dyer et al., 2022). It is important to mention that we ignore if genetic factors of the parasite can also influence the response to treatment.

Our results also found that FDC not only demonstrated a high cure rate among participants infected with *T. trichiura* but also, in contrast to albendazole, significantly reduced egg counts in 59 % of individuals who were not cured. Moreover, it exhibited satisfactory efficacy for treating hookworm infections (World Health Organization, 2013). While its efficacy against *A. lumbricoides* and *S. stercoralis* was not assessed in this study, FDC is expected to show high efficacy against these parasites as well. Therefore, our analysis at the individual level also supports the value of FDC as a superior alternative to albendazole monotherapy for STH treatment and control.

Our findings reveal a decreased efficacy of FDC in participants coinfecting with *T. trichiura* and hookworms when also infected with *S. stercoralis*. It is noteworthy that this is the first time that the possible association of *S. stercoralis* co-infection with the individual efficacy of

albendazole or albendazole/ivermectin has been analyzed. Very little is known about the possible interactions between helminths, although it is known that they can alter infections with bacteria, protozoa and viruses (Schlosser-Brandenburg et al., 2023). One potential explanation could be the significant impact of helminth infections on immune modulation, whether mediated or not by the interaction with the gut microbiome (Anuradha et al., 2016, Mishra et al., 2014). Thus, the elimination of *S. stercoralis* may disrupt the biological equilibrium, potentially creating an environment conducive to the survival of hookworms and *T. trichiura*. However, it is clear that dedicated studies are needed to analyze helminth co-infections, not only to see if they affect drug efficacy but also because co-infections lead to increased morbidity (Owada et al., 2018). Another explanation is that the bioavailability of FDC is decreased by the *S. stercoralis* population and a higher affinity for the drug. This would explain the complete elimination of *S. stercoralis* infection observed in the clinical, while failing to achieve the same outcome for *T. trichiura* and hookworm infections.

All participants who received FDC received a dose of Ivermectin equal to or greater than 200 µg/kg. This is higher than the recommended dose, however, no greater efficacy was observed in participants infected with *T. trichiura* as the dose of ivermectin increased. These findings align with the exposure-response analysis, which revealed no correlation between plasma concentration of ivermectin and cure rates (Algorta et al., 2025). However, the efficacies reported in this trial and other trials with high doses of ivermectin are higher than those reported with 200 µg/kg of ivermectin (Hürlimann et al., 2022, Matamoros et al., 2021). While this could be due to a difference in efficacy between study sites, the possible impact of doses above 200 µg/kg of ivermectin on efficacy rates should be investigated further.

Gastrointestinal adverse events such as diarrhea and abdominal pain, which were the most abundant in the clinical trial, are evidence of intestinal irritation, which might lead to increased transit and increased excretion of the study drug and may reduce the efficacy of the drug (Verhoef, 2012). However, we found no association between the presence of gastrointestinal adverse events related to albendazole or FDC and a lower response to treatment. This may be because only a minority of the study population presented adverse events and most of them were of mild severity.

This study acknowledges several limitations. One limitation is that most infections were of light intensity. While this may result in an overestimation of the ERR, it is important to recognize that in countries where mass drug administration programs have been implemented for several years, moderate or high-intensity infections are now uncommon. Consequently, this limitation restricted our ability to assess the potential impact of high infection intensities on treatment efficacy. Another limitation is the methodology for egg count assessment, as only two slides per stool sample were examined and this microscopy was limited to a single stool sample before, and a single sample after treatment. This approach makes the EPG results vulnerable to random variations in egg excretion between days, and the low sensitivity of the Kato-Katz technique in detecting light-intensity infections may further contribute to an overestimation of ERRi. However, a duplicate Kato-Katz thick smear remains the gold standard for STH diagnosis and control.

Our findings confirm that model-based analysis of ERRi is a powerful tool for gaining a deeper understanding of therapeutic failure. This approach provides an accurate, robust, and insightful measure of anthelmintic efficacy, complementing cure rate and ERR at the population level. ERRi analysis enables the identification of study populations that may exhibit a lower response to treatment, making it a valuable consideration for the design of future clinical trials and epidemiological studies. Moreover, ERRi analysis can identify participants who show significantly reduced egg counts after treatment, facilitating the selection of biological samples for future resistance studies. Also, our findings suggest the potential association between co-infections and the response to treatment with albendazole and FDC, which deserves further analysis. Additionally, we reaffirm that

albendazole remains a viable option for the treatment of hookworm infections, while FDC shows promise as a treatment for *T. trichiura*, with potential application for multiple parasite infections, such as *Strongyloides stercoralis*, onchocerciasis, lymphatic filariasis, or scabies.

Ethics approval and consent to participate

All sites approved the trial through their National Ethics Committees as well as regulatory authorities. A DSMB was established and supervised the study progress.

Consent for publication

Parents and participants were thoroughly informed about the consent process. Parents provided written consent, and participants aged 12 to 17 years signed their respective assent forms to participate in the clinical trial.

Availability of data and materials

The study protocol has been registered with ClinicalTrials.gov, NCT05124691. De-identified individual participant data will be accessible upon request following publication via the Infectious Diseases Data Observatory at <https://www.iddo.org/>. Access will be provided to investigators who submit scientifically rigorous proposals. Each proposal will undergo evaluation for scientific merit by the investigator sponsor and collaborators. Requests for data should be directed to Jose Muñoz (jose.munoz@isglobal.org).

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CRediT authorship contribution statement

Pedro E. Fleitas: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Javier Gandasegui:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis. **Woyneshet Gelaye:** Writing – review & editing, Investigation. **Augusto Messa:** Writing – review & editing, Investigation. **Stella Kepha:** Writing – review & editing, Investigation. **Lisette van Lieshout:** Writing – review & editing, Project administration. **Jaime Algorta:** Writing – review & editing, Funding acquisition. **Áuria de Jesus:** Writing – review & editing, Investigation. **Valdemiro Novela:** Writing – review & editing, Investigation. **Inácio Mandomando:** Writing – review & editing, Project administration. **Charles Mwandawiro:** Writing – review & editing, Project administration. **Wendemagegn Enbiale:** Writing – review & editing, Project administration. **José Muñoz:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Funding acquisition, Conceptualization. **Alejandro Krolewiecki:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Jaime Algorta is an employee of Laboratorios Liconsa. All other authors declare no competing interests.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.actatropica.2025.107742](https://doi.org/10.1016/j.actatropica.2025.107742).

Data availability

Data will be made available on request.

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