Ivermectin to reduce malaria transmission– safety and efficacy results from the BOHEMIA cluster randomized trial in Mozambique

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Summary

Background Endectocides are a novel vector control tool that reduce the survival and fertility of blood sucking arthropods that feed upon treated humans or animals. Ivermectin mass drug administration is under evaluation as a complementary strategy for malaria vector control. The BOHEMIA consortium conducted two cluster-randomized trials, one in Mozambique, reported here and one in Kenya, reported elsewhere.

Methods The trial was conducted in Mopeia, a highly endemic district in Zambezia province, with perennial transmission and over 70% coverage of both indoor residual spraying and long-lasting insecticidal nets. As per protocol, we planned to randomise 53 clusters per arm (1:1:1), to receive either (a) single 400 mcg/kg dose of ivermectin to all eligible humans, once a month for three months, (b) the same ivermectin treatment to eligible

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humans plus injectable ivermectin (1% solution) to all eligible pigs (300 mcg/kg) and cattle (200 mcg/kg) in the cluster once a month for three months or (c) albendazole (400 mg), to serve as control, to eligible humans, following the same schedule. The primary efficacy outcome was malaria incidence of infections determined by RDT in a cohort of children under five years that was followed monthly for six months starting with the first mass drug administration round. Dual HRP-2 and pLDH rapid diagnostic tests were used in an attempt to discriminate incident infections. The rate of adverse events was captured in all treated individuals. The analysis was done using generalized estimating equations following intention-to-treat.

Findings Before the start of mass drug administration, the study site experience floods caused by the Gombe cyclone, resulting in severe logistical constrains and the loss of 57 clusters. We present a complete case analysis of the remaining clusters. The study ran between march 17 and October 18, 2022. Overall, a total of 22,724 participants from a reduced number of 100 clusters were enrolled. Six months after the first treatment round, the malaria infection incidence was comparable between all three arms with adjusted incidence rate ratio values of 0.99 (95% CI, 0.86–1.14, $P > 0.9$) and 1.05 (95% CI, 0.87–1.27, $P = 0.6$) between the human-only and control group and the human and livestock and control group respectively. The rate of severe adverse events per 10,000 treatments was not significantly different between the combined ivermectin arms and the control (IRR = 1.29; 95% CI 0.62–2.68).

Interpretation This trial did not meet implementation goals due to operational challenges including low coverage, displaced populations and delayed start of drug distribution which render the efficacy data inconclusive. However, important aspects regarding the action of endectocides at community level which could be key for implementation are described. Additionally, valuable data regarding safety were collected (ClinicalTrials.gov number, NCT04966702).

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Keywords: Malaria; Ivermectin; Endectocides; Mass drug administration; Cluster randomized trial

Introduction

Malaria remains a major public health problem in low- and middle-income countries. There were 263 million cases and 597.000 malaria deaths in 2023 with the vast majority of disease burden occurring in the World Health Organization Africa Region.[1] Novel tools and approaches to malaria control are needed to meet the goals established for 2030 by the World Health Organization (WHO).[2]

Ivermectin is an anti-parasitic drug that is commonly used in humans against soil-transmitted helminths, river blindness, lymphatic filariasis and scabies. It also kills malaria vectors that feed on treated humans or animals in a concentration-dependent manner.[3] Mass drug administration (MDA) with ivermectin has been suggested as a complementary strategy against malaria vectors with behavioural traits that hamper control through current indoor-centred methods such as long-lasting insecticide-treated nets and indoor residual spraying (LLINs and IRS).[4–6]

In the past nine years, four cluster-randomized clinical trials in three African countries have attempted to assess the impact of ivermectin on malaria transmission.[7–10] These trials have used different ivermectin doses along with varying drug combinations, such as seasonal malaria chemoprophylaxis or MDA with an antimalarial, as well as different outcome measures, which makes a joint analysis challenging.

The Broad One Health Endectocide-based Malaria Intervention in Africa (BOHEMIA) consortium conducted two independently powered, controlled, cluster randomized trials in different eco-epidemiological settings in Kenya and Mozambique.[11] These trials used ivermectin-only as an intervention to evaluate the individual potential of ivermectin for vector control. This work aimed to generate the evidence required for policy makers to make an informed decision.

The Kenya trial was conducted in Kwale county, which has the highest malaria burden in the coastal region. The baseline prevalence was 30% by RDT despite 80% ownership and usage of LLINs. The trial met all the operational targets set in terms of timeliness of MDA against the rains (MDA started before rains), acceptability and population coverage (at least 64% of overall population treated). The Kenya study found that a single 400 mcg/kg dose of ivermectin, distributed monthly for three months had an incremental 26% reduction in malaria infection incidence in a cohort of children 5–15 years old. No safety concerns were identified.[12] Here we report the safety and efficacy results of the Mozambique trial, which had the same design, dose and outcome measure, yet faced severe

Research in context

Evidence before this study

We searched PubMed on August 2025 without date or language restrictions using the terms "ivermectin", "malaria" and "cluster". Five cluster-randomized clinical trials have evaluated ivermectin MDA as a malaria control strategy using different ivermectin doses, antimalarial combinations and outcome measures. The RIMDAMAL trial, conducted in Burkina Faso, randomized eight clusters to either a single oral dose of ivermectin (150–200 μg/kg) plus albendazole 400 mg at baseline (control) or five additional ivermectin-only doses (150–200 μg/kg) every three weeks. The primary outcome measure was uncomplicated malaria clinical incidence (fever plus a positive RDT) in children under 5, throughout the 18 study weeks. The reported 20% reduction has been disputed due to its small sample size. The MASSIV trial, conducted in The Gambia, randomized 32 villages to three monthly rounds of ivermectin (300–400 μg/kg per day for 3 consecutive days) plus dihydroartemisinin-piperaquine (DHAp) in combination with LLINs and IRS, or LLINs and IRS without community-wide drug-based interventions (except SMC in eligible children) in the control arm during two consecutive years. The primary outcome measure was malaria prevalence by qPCR (all ages) at the end of the intervention in the second year. The study found a 60% reduction in the intervention group. The design, however, does not allow to discriminate the role of ivermectin in this outcome. The MATAMAL trial, was conducted in the Bijágos Archipelago, Guinea-Bissau. A total of 24 clusters were randomized to three monthly MDA rounds of DHAp, with the intervention arm additionally receiving ivermectin MDA (300 μg/kg per day for 3 consecutive days). The trial was done over two consecutive years. The primary outcome measure was malaria prevalence by qPCR (all ages) during the peak transmission season after the second year. The study was powered to detect an incremental 50% reduction from expected 10% in the DHAp arm to 5% in the DHAp-IVM arm. The prevalence in the DHAp arm after two years was 5% instead of the expected 10% and the study failed to show an incremental 50% reduction in the ivermectin group for which it had been powered. RIMDAMAL II, was conducted in the same region of Burkina Faso as RIMDAMAL. This trial randomized 14 clusters to receive three monthly rounds of ivermectin (300 μg/kg per day for 3 consecutive days) or placebo along with seasonal malaria chemoprevention administered to some 45% of the eligible children in both arms. The trial was implemented for two consecutive years. The primary outcome measure was uncomplicated malaria clinical incidence (fever plus a positive RDT) in children under 10 throughout the eight peak transmission months in two consecutive years (45% of the cohort -those under 5 years of age-received SMC). The national malaria control program conducted a mass distribution of second-generation bed nets (Interceptor G2) in all study villages in between the two study years. The observed malaria incidence in the control group was 1.84 per 100 person-weeks at risk instead of the expected 2.04 which was used for powering the study, and it failed to show a difference between the groups which had been estimated at 43% by modelling. Finally, the BOHEMIA trial in Kenya, was conducted in Kwale, coastal region and randomized 84 clusters to receive a single monthly dose of ivermectin (400 mcg/kg) or albendazole (400 mg) as control, it included no other pharmacological intervention. The primary outcome measure was malaria infection incidence in children 5–15 tested with an RDT monthly for six months starting with the first MDA round. The study found a statistically-significant 26% reduction in the malaria infection incidence in the ivermectin arm.

Added value of this study

The implementation of this study was severely disrupted due to extreme weather events which prevents a full interpretation of the results. It provides however, important insight into the implementation variables affecting the efficacy of ivermectin MDA in the field, including the timing against the start of the rains, the coverage at population level and the speed of the roll-out. It also contributes to more than 57.000 treatment observations of a single 400 mcg/kg dose to the safety database.

Implications of all the available evidence

Ivermectin MDA was proven efficacious to reduce malaria transmission in addition to LLINs by the BOHEMIA trial in Kenya, conducted after the trial presented here. The recent cluster-randomized clinical trials combining ivermectin MDA with additional drug-based strategies in the community have faced operational challenges which given insights described in this study, could partly explain the lack of measurable effect. Additional evidence, collected using comparable study designs, will be required to assess the efficacy of ivermectin on its own or combined with other interventions.

operational constraints caused by an extreme weather event. We describe how the implementation differences between the trials in Mozambique and Kenya can be leveraged to inform the design of any upcoming trials evaluating this potential new approach to vector control.

Methods

Study site

Mopeia is a rural district in Mozambique with a population of 131,818 and a very high malaria burden, with parasite prevalence by RDT exceeding 60% in children in previous cross-sectional studies.[13] Malaria causes 40% of all mortality in children under five in Mopeia,[14] and is associated with high direct and indirect costs at the household level.[15] Mopeia receives both IRS from the US President Malaria Initiative (PMI)[16,17] (Bendiocarb in 2021) and mass distribution of LLINs, with the last one occurring in August 2020, 17 months before study start (Pyrethroid-only, Olyset ™). In March 2021 (one year before the study started), 71% of all households reported having received IRS in the previous 12 months and over 90% of households reported owning at least one LLIN, with 54% of those owning at least one LLIN for every two household members.[14] Mopeia is endemic for lymphatic filariasis[18] and had not received MDA with ivermectin or albendazole since January 2020.

Study design

In Mozambique, BOHEMIA was a three-arm, parallel-group, open-label, assessor-blinded, superiority, cluster-randomized controlled trial. The unit of randomization was the cluster, and the unit of analysis for efficacy was children under 5 years of age living in the clusters. The unit of analysis for safety was all participants receiving at least one dose of the study drugs.

Between October 2020 and March 2021, the study team mapped and enumerated all households and residents in Mopeia. With these data, 159 clusters were created using a computer algorithm. A "fried egg" design was used to define the spatial layout of each cluster and divide it into core and buffer areas. Each cluster consisted of a core area, which included all households where at least 20 children under five lived and a surrounding buffer zone encompassing all households within a 400-m radius around the core. The minimum distance between two core areas was 800 m.

In preparation for the trial, all households in the clusters were visited between June and November 2021, and data on health system usage, disease burden and malaria protective measures were collected. A separate community engagement team met with every community leader and held open community information sessions where the objectives, risks and benefits purpose of the trial were presented. All questions were answered in the local language and any potential concerns addressed. All data were collected using Android tablets to complete digital forms with built-in quality assurance checks created in Open Data Kit (ODK, https://opendatakit.org).

Randomization and masking

Clusters were assigned 1:1:1 by simple randomization into the three study arms using a computer-generated algorithm by an independent data scientist. Assignments were revealed to the study population during a community-engagement ceremony conducted by the community engagement team.

The study was open-label and assessor-blinded; that is, the participants were informed they were taking one of two anthelminthics and received products that differed in aspect and numbers. The sponsor team and study statistician remained blinded to group assignments until the last visit of the efficacy cohort.

Eligibility

Two cohorts were created and followed prospectively within the clusters across the three trial arms: a safety cohort, composed of all those who received at least one dose of treatment, and an efficacy cohort, composed of children under five years of age in which malaria infection incidence was measured.

The safety cohort included all consenting residents in the study area who weighed at least 15 kg, had no travel history to *Loa loa* endemic areas, were not taking treatment with potential for drug–drug interactions, and were not severely ill. All women of reproductive age participating in the study were advised to avoid pregnancy during their participation and were offered referrals to family planning services. Women aged 13–49 needed to take a pregnancy test and have negative results before each treatment round. Those found pregnant in a subsequent visit after dosing were included in a pregnancy cohort, did not receive further treatment, and were followed up monthly until pregnancy outcome.

Participants or their legal guardian in all cohorts provided written informed consent. All adolescents aged 13–17 provided informed assent. Informed consent was also sought from the owners of treated livestock. No incentives were offered to the participants. The full details of the inclusion and exclusion criteria are provided in the Supplementary Appendix.

Intervention

There were three treatment groups: (a) human-only ivermectin group, (b) human and livestock ivermectin group and (c) human-only albendazole group (control).

The ivermectin dosing was guided by mathematical modelling[19] as well as a PK/PD trial conducted in coastal Kenya which showed compared the 400 mcg/kg single dose to the 300 mcg/kg for three consecutive days dose, and confirmed the lack of mosquitocidal effect of albendazole. The single dose was non-inferior in killing mosquitoes fed on treated volunteers for the first 21 days after treatment; indeed, it showed a remarkable 5-fold mosquitocidal activity in killing mosquitoes feeding on treated volunteers for the first 10 days after treatment and remained superior to the triple dose for the first two weeks.[20]

Group (a) received 400 mcg/kg of ivermectin (Stromectol®, from MSD, The Netherlands, supplied in 3 mg tablets) once a month for three months; group (b) received the same treatment plus all pigs and cattle in the area were injected with a 1% veterinary formulation (generic, Interchemie, The Netherlands) at a 200 mcg/kg dose for cattle and 300 mcg/kg dose for pigs, monthly for three months; group (c) received albendazole 400 mg fixed dose (generic chewable tablets from Cipla, India), once a month for three months. The product manufacturers had no role in the trial. Albendazole was used in the control group to provide participants with the known deworming benefit of ivermectin and increase comparability.

The target treatment coverage was 80% of the eligible population, estimated at 64% of the general population. This was based on mathematical modelling and the usual operational targets of the Mectizan Donation Program.

Treatment was administered door-to-door and directly observed by field workers residing in the clusters. At every study visit, a questionnaire was administered to all participants. For those in the safety cohort, this included specific and open questions on the potential adverse events (AE) experienced between visits. Study personnel were always available at the cluster level through the resident field worker. Additionally, a toll-free phone line was available for any concerns from study start until one month after the last treatment round. The medical team and field supervisors visited the district hospital and health facilities to ensure all potential AEs were appropriately documented.

Primary outcomes

The primary outcome measure for efficacy was infection incidence rate ratio (IRR) in the cohort of children under the age of five, followed prospectively for six months starting at the time of the first study dose in their cluster. Children were tested monthly for infection using WHO-prequalified rapid diagnostic tests based on both parasite lactate dehydrogenase (pLDH) and histidine-rich protein 2 (HRP-2). The incident case definition relied on both tests, and the infection and treatment status of the child's previous visit (Supplementary figure 1). This was done to distinguish novel infections from residual HRP-2 antigen which can persist for up to six weeks in 50% of infections, while pLDH results are normally negative within 48 h of treatment.[21] Asymptomatic children with HRP-2 positive but pLDH negative tests were not considered to have an incident infection as long as they had proof of treatment in the last month. Artemether-lumefantrine (AL) provides 2 weeks of prophylaxis,[22] this, together with a pre-erythrocytic stage of 5–14 days[23] greatly reduces the possibilities of inter-visit infections in these treated children. All children with a positive result in either test component received treatment with AL according to the national guidelines. The

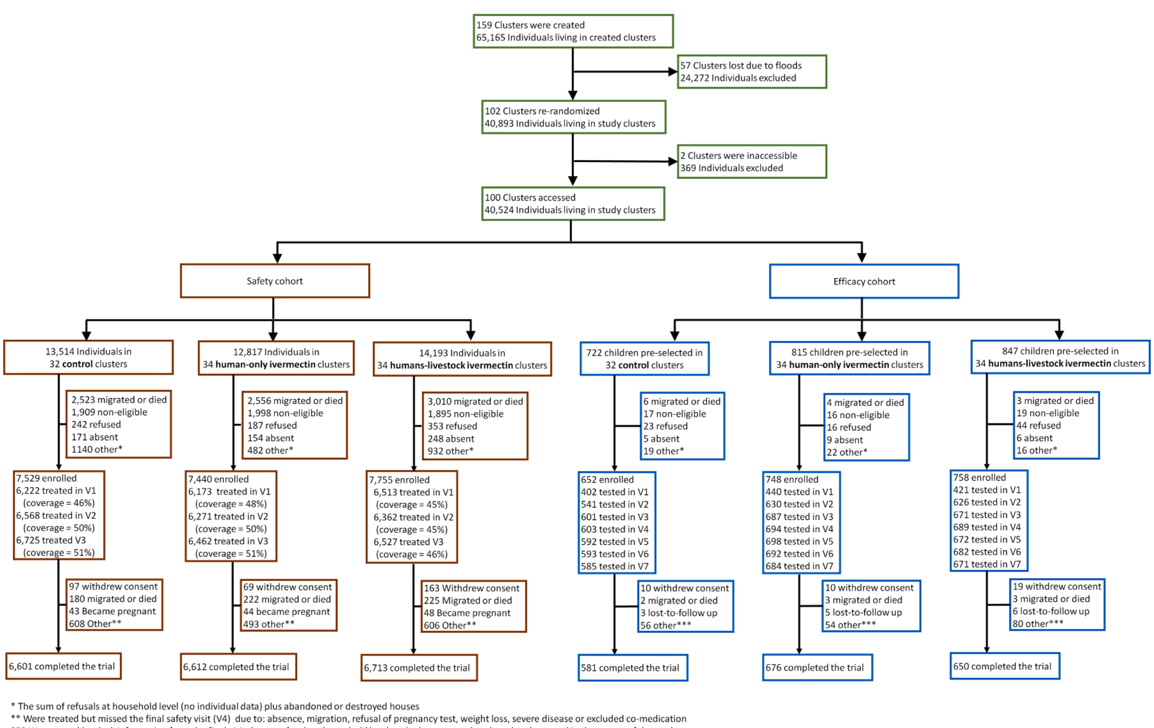


Fig. 1: Enrolment, randomization and follow up of treated participants and children in the cohort. There were two cohorts of participants. Those receiving the drug comprise the safety cohort, their eligibility was primarily based on weight (>15 kg). Those in which the efficacy outcome of infection incidence is determined comprise the efficacy cohort, their eligibility was based on age (<5 years of age). The small discrepancies with figure two on the number of children tested in every visit are due to some failed tests or invalid RDT results.

first dose was always directly observed by a field worker. Only those fulfilling all of the following criteria were untreated: (a) had a pLDH-negative/HRP-2-positive result (b) had received AL treatment in the previous two weeks and (c) had proof at hand in the form of a medical prescription or empty blisters. All children with symptoms were referred to the nearest health facility for medical evaluation. The time at risk of every child was adjusted for the prophylaxis provided by AL treatment.[22] All field visits with a valid RDT result from enrolled children were included in the analysis.

The primary safety outcome was defined as the IRR of AEs and severe adverse events (SAEs) between the pooled ivermectin arms compared to the control arm. No changes to trial outcomes were made after the trial started and the statistical analysis plan (SAP) was locked before completing enrolment. All participants taking at least one dose of the study drugs were included in the safety analysis.

Trial oversight

The trial design was reviewed by an advisory committee and by the WHO vector control advisory group (VCAG) who approved the study before starting enrollment.[24] The data and safety monitoring board (DSMB) reviewed all safety reports and met regularly throughout the study period.

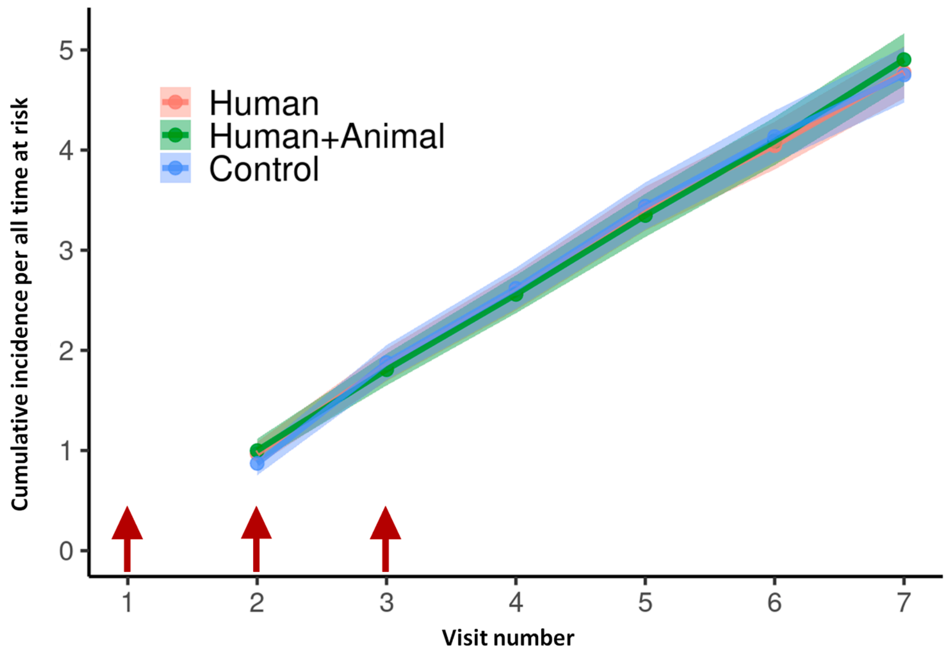
The trial was conducted under Good Clinical Practice (ICH-GCP) guidelines, and Mozambican law. The protocol was reviewed and approved by the National Committee for Health Bioethics of Mozambique (618/CNBS/21), the Institutional Review Board of the Hospital Clinic of Barcelona (HCB/2019/113) and the World Health Organization Research Ethics Review Committee (ERC.0003574). Additional approval was obtained from the National Medicines Regulatory Authority of Mozambique (8309/380/DNF). The trial was registered on clinicaltrials.gov (NCT04966702) and on the Pan African Clinical Trial Registry (PACTR202106695877303).

The protocol has been published[11] and is available in the supplementary materials to this manuscript. All authors had access to the data and vouch for the accuracy of the data and for the fidelity to protocol. The first author wrote the initial draft of the manuscript. All authors contributed to revisions and agreed on

Variable[a]	Ivermectin in humans	Ivermectin in humans and livestock	Albendazole
Overall treated population			
Mean female (%)	49.2 (47.6–50.9)	50.4 (48.8–51.9)	49.3 (47.7–50.9)
Mean age (years)	24.5 (24.1–25)	24.4 (24–24.8)	24.2 (23.8–24.6)
Children in the efficacy cohort			
Mean female (%)	49.1 (45.5–52.7)	48 (44.4–51.6)	47.9 (44.0–51.7)
Mean age (years)	2.9 (2.8–3.0)	3.0 (2.9–3.1)	3.0 (2.9–3.1)
Median distance to cluster border (m)[b]	225 (92.9–326.2)	244.5 (97.9–349.0)	226 (77.7–327.7)
Median baseline RDT positivity rate (%)	67.7 (43.2–79.4)	55 (46.2–75.0)	62.9 (43.6–80.0)
Cluster population			
Median density (persons/km^2)	188 (85–313)	177 (76–297)	214 (110–299)
Wealth index rank			
Low (%)	33.8 (30.4–37.2)	33.0 (29.7–36.4)	27.5 (24.1–30.9)
Medium (%)	38.9 (35.4–42.4)	40.7 (37.2–44.3)	44.5 (40.7–48.4)
High (%)	27.3 (24.1–30.5)	26.2 (23.1–29.4)	28.0 (24.5–31.4)
Livestock presence	0.8 (0.1–1.5)	0.3 (0.1–0.6)	0.3 (0–0.5)
Mean livestock (cattle & pigs) to 100-humans ratio			
LLIN usage at cluster level			
Median proportion that slept under a LLIN the previous night (%)	88.4 (66.4–98.6)	91.2 (75.4–96.3)	88.6 (73.6–93.7)
Implementation details			
Mean coverage of 3 rounds (%)	48.6 (45.8–51.5)	48.2 (45.2–51.2)	49.5 (46.6–52.4)
Mean MDA duration (days)	18.2 (16.2–20.1)	18.5 (15.8–21.1)	16.9 (14.7–19.1)
Environmental variables			
Median rainfall (mm)	16.2 (9.0–69.7)	17.0 (9.8–70.9)	16.5 (7.5–71.6)
Median daily temperature (Celsius)	26.3 (24.4–27.6)	26.3 (24.2–27.5)	26.1 (24.3–27.6)
Household-months with water bodies within 500meters[c]	31	31	18
Household-months without vegetation within 500meters[d]	0	0	0

[a]In parentheses are 95% CI for means and Q1-Q3 for medians, the distribution of all variables is provided in the supplementary appendix, coverage is based on the total population enumerated. [b]Distance from the household where the cohort child lives to the geographic border of the cluster. [c]Sentinel-2 water index (SWI) 0.2–1. [d]Normalized Difference Vegetation Index (NDVI) $\geq$ 0.2.

Table 1: **Baseline characteristics and implementation details per study arm.**



	1	2	3	4	5	6	7
Ivermectin in H							
Children tested	431	622	671	684	698	692	684
Cumulative cases		265	507	708	934	1,106	1,306
Ivermectin in H+L							
Children tested	421	619	667	688	672	685	671
Cumulative cases		275	498	705	922	1,126	1,350
Albendazole							
Children tested	396	541	600	602	592	593	585
Cumulative cases		207	446	622	817	982	1,128

Fig. 2: Efficacy of ivermectin vs. albendazole. Shown is crude cumulative malaria infection incidence in the six months following the start of three, monthly rounds of ivermectin MDA at a 400 mcg/kg single dose vs. albendazole at a dose of 400 mg (MDA timing indicated by red arrows). Infections were detected by means of WHO-prequalified dual RDTs (Standard Q Malaria, SD Biosensor, Suwon-si, Republic of Korea) based on parasite pLDH and HRP2 to help differentiate between new infections from antigen persistence. All children with positive results received treatment with artemether-lumefantrine and their time at risk was adjusted to account for 14 days of prophylaxis after every treatment. Shaded areas indicate crude 95% confidence intervals. Crude confidence intervals are not adjusted for clustering and are provided for descriptive purposes.

submitting the manuscript for publication. The trial was funded by Unitaid under the BOHEMIA grant and sponsored by ISGlobal.

Statistical analysis

The study was originally powered to detect a 20% reduction in infection incidence based on the 2017 minimally-acceptable criteria of the WHO Preferred Product Characteristics (PPC) for endectocides.[25] We calculated that 159 clusters, each containing at least 20 eligible children, followed up for six months, were needed to detect a 20% reduction in the primary efficacy outcome, from 4.2 in the control group to 3.36 infections per child/year-at-risk in the human-only ivermectin group. The coefficient of variation used was 0.35. For the human and livestock intervention the sample size was powered to detect an incremental 20.5% reduction from 3.36 infection per child/year-at risk in the human-only arm to 2.67 in the human and livestock arm.

The cluster size allowed for three recruitment failures and three children lost to follow-up. There were three additional clusters in case of cluster level attrition. We estimated the average cluster size to be 300 participants eligible for treatment.

The pre-specified efficacy and safety intention-to-treat analysis was a Poisson regression model using generalized estimating equations (GEE) with exchangeable correlation structure to estimate the differences in cumulative malaria infection incidence and AE rates across study arms. Co-variate categories were

Characteristic	All covariates		P-value	Final model		P-value
	IRR	95% CI		IRR	95% CI	
Assignment						
Albendazole	–	–	–	–	–	
Ivermectin in humans	**1.02**	**0.88–1.17**	**0.8**	**0.99**	**0.86–1.14**	**>0.9**
Ivermectin in humans and livestock	**1.07**	**0.90–1.29**	**0.4**	**1.05**	**0.87–1.27**	**0.6**
Age group of cohort children						
Under 2	–	–	–	–	–	
2 to 4	1.08	0.99–1.18	0.08	–	–	
Over 4	0.98	0.89–1.07	0.7	–	–	
Sex of cohort children						
Female	–	–		–	–	–
Male	1.06	1.00–1.12	0.03	1.06	1.01–1.12	0.03
MDA duration[a]						
<10 days	–	–	–	–	–	
>10 days	1.02	0.89–1.17	0.7	–	–	
Distance to cluster border of cohort children[b]						
<367 m	–	–	–	–	–	
>367 m	1.07	0.97–1.18	0.2	–	–	
LLIN usage at cluster level[b]						
<89%	–	–	–	–	–	
>89%	1.00	0.87–1.14	>0.9	–	–	
Cluster population density[b]						
<355 persons/km^2	–	–	–	–	–	
>355 persons/km^2	0.82	0.67–0.99	0.04	–	–	
Treatment coverage at cluster level[b]						
<55%	–	–	–	–	–	
>55%	0.99	0.84–1.16	0.9	–	–	
Livestock/human ratio at cluster level[a]						
= 0	–	–	–	–	–	
>0	0.85	0.72–1.01	0.06	–	–	
Wealth index[c]						
Low	–	–	–	–	–	–
Medium	0.90	0.81–0.99	0.03	0.89	0.81–0.98	0.02
High	0.87	0.76–0.99	0.03	0.84	0.74–0.96	0.01
Baseline prevalence in cohort children[a]						
<63.4%	–	–	–	–	–	–
>63.4%	1.17	1.01–1.35	0.03	1.24	1.08–1.42	0.002
Environmental variables[d]						
Cumulative rainfall	1.00	1.00–1.00	0.07	–	–	
Mean day surface temperature	1.00	0.98–1.01	>0.9	–	–	
Presence of water bodies	0.90	0.71–1.13	0.4	–	–	
Presence of vegetation	–	–		–	–	

The results of the primary comparisons are bolded. [a]Above and below the median. [b]Above and below the 80th percentile. [c]Tertiles, calculated according to Xie et al.[28] [d]Continuous quantitative for increases of one mm or Celsius degree for rainfall and day temperature respectively, presence/absence for water bodies (Sentinel-2 water index >0.2) and presence of vegetation (Normalized Difference Vegetation Index >0.2), 100% of households had NDVI >0.2 throughout the study. The full information and distribution of each variable is provided in the supplementary appendix.

Table 2: **Poisson regression models for malaria infection incidence fitted with generalized estimating equations. Results with all covariables and stepwise selection are shown.**

pre-specified in the SAP and a stepwise approach was used to build the final multivariable model. Hypothesis testing was two-sided and significance was set at 0.05. No interim analyses were performed.

Operational data and comparison with Kenya

The following parameters were collected during study roll out and compared across the trials in Kenya and Mozambique and analysed post-hoc as they can offer insight into the critical parameters affecting the efficacy of endectocides against malaria at community level: (a) relative start of MDA vs. start of the rains, (b) drug coverage at population level, (c) time taken to distribute the study drugs, (d) relative time of outcome measure capture (testing of children in the cohort) vs. MDA roll-out, and (e)

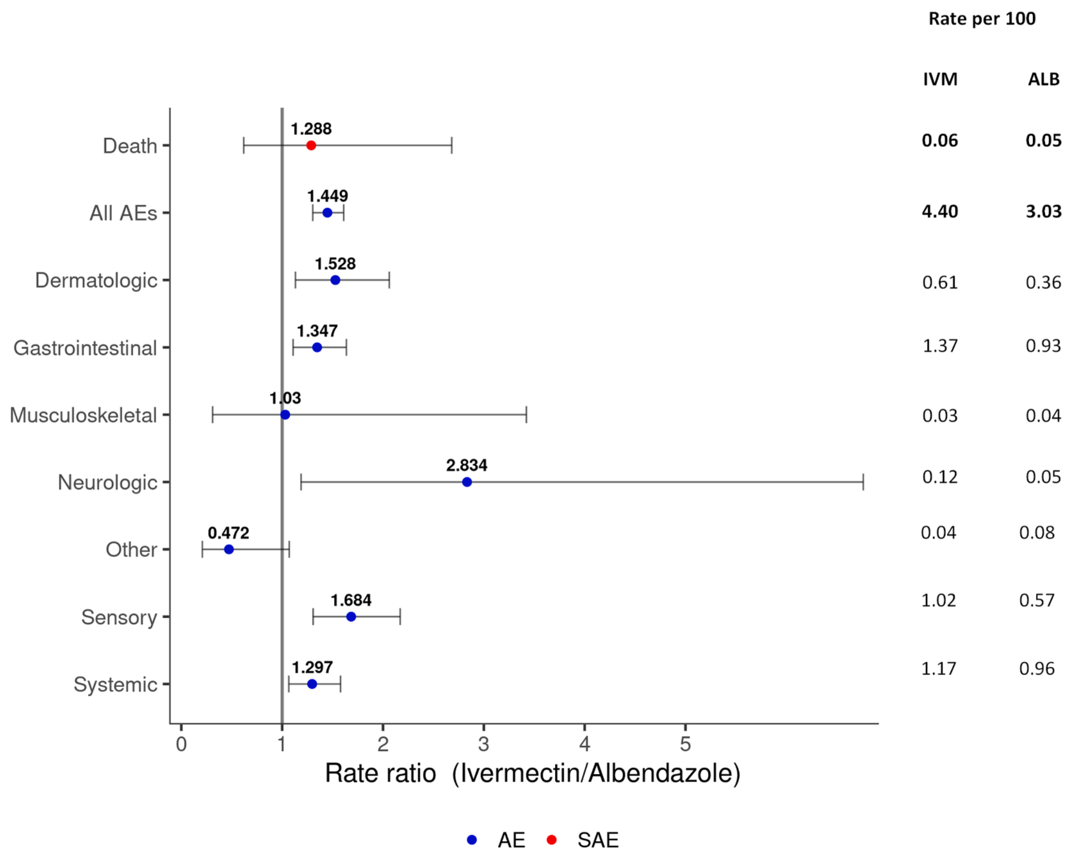


Fig. 3: Safety of ivermectin vs. albendazole. Pre-specified safety outcome measures, the incidence rate ratio of SAEs and AEs by body system. There were 35 non-pregnancy-related SAEs among 35 participants, all deaths (25 in the two combined ivermectin arms), none deemed drug-related by the medical monitors. There were 2277 AEs among 1302 participants (1685 AEs among 38,308 ivermectin treatments and 592 among 19,515 albendazole treatments). The AE categories with a statistically-significant difference between groups were systemic, sensory, neurologic, gastrointestinal and dermatologic, none occurred in more than 1.4/100 treated. There were 705 gastrointestinal AEs, of these, 467 (66.2%) were abdominal pain, 215 (30.4%) were vomiting. There were 638 systemic AEs, 628 (98.4%) were fever. There were 503 sensory AEs, of these, 327 (65.0%) were vertigo and 175 (34.7%) were visual disturbances. There were 306 dermatologic AEs, 299 (97.7%) were itchiness. There were 58 neurologic AEs, 56 (96.5%) were headache.

relative distance to cluster border of children in the cohort. This information was plotted incorporating the number of rounds, the roll out speed and the coverage.

Role of the funding source

The funder had no role in the study design, conduction or decision to submit the manuscript for publication.

Results

Participants and study cohorts

The trial was scheduled to start on March 14, 2022. However, cyclone Gombe made landfall at peak intensity in Mozambique on March 11, 2022 affecting the provinces of Nampula and Zambezia.[26] It caused severe floods and structural damage in Mopeia including the collapse of bridges on the main road, which displaced the population of several villages and left the whole south of the district inaccessible for weeks. This resulted in the study team being unable to access 57 clusters, encompassing 24,272 eligible population before MDA start. These clusters, where no drug was distributed and no trial data was ever collected, were dropped and the remaining 102 clusters were re-randomized before the start of MDA. The field team was able to start operations in 70 clusters during on March 17, but access to the remaining 32 was delayed by a further month due to the state of the roads. Ultimately, 100 clusters with an eligible population of 40,524, were included (Fig. 1). In the weeks following the floods, there was a cholera outbreak in Mopeia that further hampered operations, slowing the roll out of treatment and follow-up of children in the efficacy cohort with 22,724 enrolled participants and treatment coverages per round typically under 50%.[27] The trial was completed on October 18, 2022. We present here a complete case analysis of the resulting 102 clusters.

The baseline characteristics and operational variables such as coverage and roll-out time cross groups

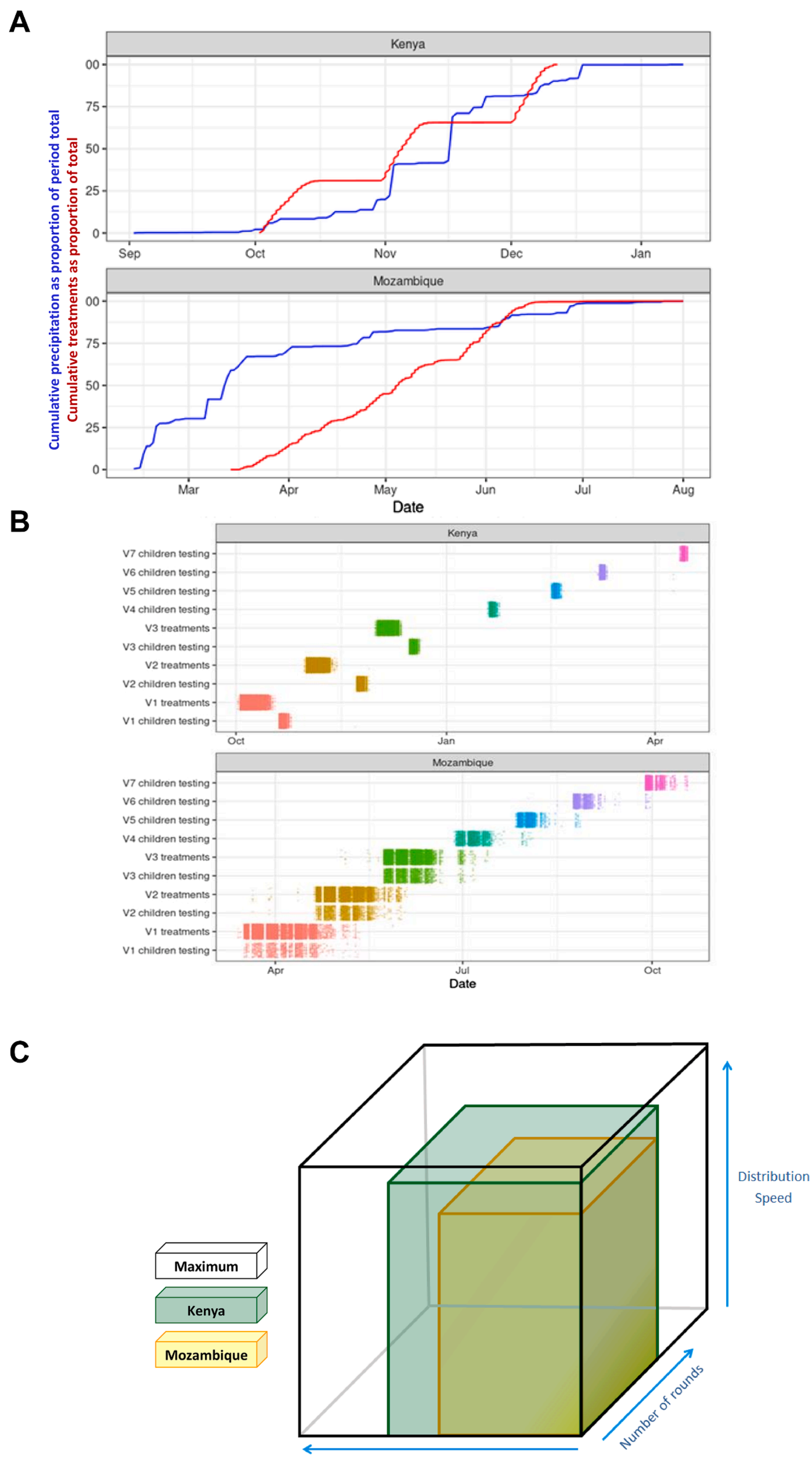


Fig. 4: Operational comparison between Mozambique and Kenya. Panel **A** shows the cumulative daily rains (blue) and the cumulative treatments given every day (red). Note how operations in Kenya ensure almost two full rounds of drugs distributed before 50% of the

are presented in Table 1. The reduced number of clusters left the study with 60% power to detect a 25% difference in the efficacy outcome measure as opposed to the originally planned 20%.

Primary efficacy results

The crude infection incidence was 4.75 infections/child-year-at-risk in the albendazole arm, 4.77 in the human-only ivermectin arm, and 4.90 in the human and livestock ivermectin arm (Fig. 2).

An independence correlation structure was used in the GEE model as the exchangeable structure prevented conversion. The statistical model incorporating the pre-specified covariates using a stepwise procedure renders an incidence rate ratio of 0.99 (95% CI, 0.86–1.14, P > 0.9) between the human-only and control group and 1.05 (95% CI, 0.87–1.27, P = 0.6) between the human and livestock and control group (Table 2).

Primary safety results

The 22,724 enrolled participants (15,195 in the combined ivermectin arms) received 57,823 individual treatments (38,308 in the combined ivermectin arms). There were 2277 AEs among 1302 participants (1685 AEs in the combined ivermectin arms). The rate of AEs per 100 treatments was 2.96 (95% CI 2.73–3.20) in the albendazole and 4.3 (95% CI 3.95–4.76) in the combined ivermectin arms. The ivermectin/albendazole IRR for AEs was 1.47 (95% CI 1.33–1.61, P = 0.005). This is mainly driven by the AEs categorized as systemic, sensory, neurologic, gastrointestinal, and dermatologic (Fig. 3). The full safety details are provided in the Supplementary Appendix.

There were 135 pregnancies potentially exposed to the study drugs during the trial (93 in the combined two arms receiving ivermectin and 42 in the control), no safety signal was found in this group, these results are reported separately. There were 35 non-pregnancy related SAEs, all were deaths (10 in the albendazole arm, 15 in the ivermectin in the human-only arm and 10 in the ivermectin in the humans and livestock arm). None were deemed drug-related by the medical monitors. The rate of SAEs per 10,000 treatments was 5.12 (95% CI 2.69–9.30) in the albendazole control arm, and 6.52 (95% CI 3.09–13.42) in the combined ivermectin treatment arms. The ivermectin/albendazole IRR for SAEs was 1.29 (95% CI 0.62–2.68, P = 0.4) (Fig. 3).

Operational data and comparison with Kenya

The timing of the intervention as compared to the start of the rains was drastically different between the two trials: two full rounds of treatment were distributed in Kenya before the rains peaked, while in Mozambique, the first dose was distributed well after peak (Fig. 4A). Treatment coverage in the ivermectin arm was 62–68% in Kenya and 45–51% in Mozambique. In Kenya, drug distribution was completed in a mean of 10 days (95% CI 8.7–10.7) with 6–9% of the target population treated every day, resulting in three discrete rounds, while in Mozambique the teams rarely treated more than 4% of the target population on any given day with distribution lasting 18.2 days (95% CI 16.2–20.1), making it challenging to differentiate treatment rounds from one another (Fig. 4A). The study visits in Mozambique combined consent taking, treatment and child testing: this meant that the proportion of participants treated before testing of the first child in Mozambique was below 1% while in Kenya, treatment and testing visits were separate, meaning that a full round of MDA was distributed some 2 weeks in advance of the testing of the first child (Fig. 4B). Regarding the combined analysis of operational metrics, if we consider five rounds in which the current ivermectin dose and formulation is distributed within a single day to 100% of the population as a theoretical (unattainable) limit, then the Kenya trial reached almost 40% of that limit, while Mozambique did not achieve even 25% (Fig. 4C). Finally, the median distance to cluster border of children in the ivermectin arms in Mozambique was 225–226 m (IQR 77–326) while in Kenya this distance was almost double at 395 m (IQR, 384–422).

Discussion

There is a sharp contrast between the implementation of the BOHEMIA trial in Kenya, where an incremental 26% reduction in malaria infection incidence was seen in a highly endemic district with good LLIN coverage and usage, and the Mozambique trial reported here which failed to achieve implementation targets. There are, however, important insights on operations and how they may have impacted the efficacy of MDA with an endectocide.

cumulative rains fall, while in Mozambique almost 75% of the cumulative rains had fallen by the time drug distribution started. Panel **B** shows the days taken to distribute the drug and test all children in the cohort by country. Note how in Kenya, all drug is distributed in discrete rounds lasting some 10 days, making the overall ivermectin concentration at community level higher, while in Mozambique drug distribution lasted consistently longer than 20 days, with rounds sometimes overlapping with the next one, this asynchrony dilutes ivermectin concentrations at community level; similarly, the cohort children were tested in about five days in Kenya, this provided a sharp estimate of incidence in every round, while in Mozambique testing was slow, resulting in a blurred incidence estimate. Panel **C** shows a volumetric analysis along three key axes for an endectocide, coverage, distribution speed and number of rounds, if the maximum theoretical limit is derived from a 10 in all axis (5 rounds, 100% coverage, distributed in a single day), then the outer box has a volume of 1000 while Kenya has a volume of 375 and Mozambique a volume of 246.

Several factors caused the failed implementation in Mozambique and can explain the contrasting results between similar studies. Firstly, the late roll-out of MDA after the peak of the rains, while the Kenya study fully encapsulated the peak of the rains during the three rounds, Mozambique did not start drug distribution until after the rains had peaked. Supplementary figure 25 shows how the first round of MDA in Mozambique was distributed as the main local vectors *Anopheles gambiae* and *Anopheles funestus* had already reached maximum densities. Secondly, the low coverage of the Mozambique MDA, combined with the slow roll-out, greatly reduced the maximally attainable community effect by allowing the local vectors to feed upon the untreated population and sustain transmission. Thirdly, in Kenya, all children in the cohort were consistently tested within five days and always after reaching the maximum coverage, which allowed for a very sharp snapshot of the impact on transmission of every MDA round. In contrast, in Mozambique testing occurred while treatment was still being rolled out. This overlap between testing and drug administration resulted in incidence estimates that did not consistently reflect the effect of the MDA, since children were tested at varying times, corresponding to different levels of community coverage. Finally, the Kenya clusters were more densely populated and the distance to the cluster border of cohort children was almost doubled, which meant that children in Kenya were surrounded by more treated people and lived further into the clusters, something that could have provided higher protection.[29]

Regarding potentially relevant vector-related variables. If we take baseline prevalence in the children cohort as a proxy for the vectorial capacity in each site, biting pressure was much higher in Mozambique than in Kenya, making it harder for any vector control tool to reduce transmission, which is evident as Mopeia remains highly endemic despite dual coverage with LLINs and IRS.[13] Additionally, ivermectin shares some metabolic pathways with pyrethroids and other public health insecticides; malaria vectors in Mopeia had higher levels of insecticide resistance which was often metabolically mediated[30] than the vectors in Kwale,[31] whether this could have had a role in the observed results would require additional experiments. Also, although both districts have the same primary vector species, it is possible that their feeding preferences in terms of timing, location around human settlements and human blood index may affect the efficacy of ivermectin MDA, additional data would be needed to further discern the potential role of these variables.

Beyond the operational lessons learned and the insight into how the community effect is reached, the trial reported here had an important impact on scabies (Furnival Adams et al. in press) and headlice[32] which was key for perception of value and acceptability at community level. Additionally, the absence of a safety signal and an AE pattern matching both, the well-known safety profile of ivermectin in MDA for Neglected Tropical diseases (NTDs),[33] and the AE pattern seen with the same dose in Kenya,[12] provide reassurance on the safety of this drug and suggest filarial infections, known to be endemic in Mopeia, could have played a role in AEs such as itchiness, fever or general malaise seen immediately post-treatment and often associated with parasite death, the decrease of AEs over the three rounds may support this hypothesis.

Progress against malaria has been stagnant since 2015. The recent cuts in global funding for malaria threatens further reversal and sheds uncertainty around the continuation of key bilateral and multilateral global health programs. In this context, endemic countries are likely to commit more domestic funding to combat malaria. Ministers of health and managers of national malaria control programs will require good evidence on the tools currently available and potentially new ones. Cost efficiency by integrating efforts across programs will be highly desirable. Ivermectin offers a key opportunity for the malaria and NTDs community to work together. The four other trials that have looked at adding ivermectin to other drug-based interventions at community level have been discussed in the research in context panel.[7–10] The different designs, doses, drug combinations and outcome measures, together with the particular challenges faced by these other studies make operational comparisons difficult. The Mozambique trial reported here, together with the data from the separate, comparable trial in Kenya, offer valuable operational lessons for additional evaluations of endectocides as a potential, complementary integrative approach to malaria and NTDs.

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Data sharing statement

This study was sponsored by an academic institution (ISGlobal), all investigators had access to the raw data and were free to participate in data analysis and result interpretation. CCh and MR can vouch for the accuracy of the underlying data. All data and code relevant to this article will be publicly available three weeks after publication in the Dataverse of the University of Barcelona (https://dataverse.csuc.cat/dataverse/bohemia).

Declaration of interests
All authors declare no competing interests.

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Appendix A. Supplementary data
Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2025.103632.

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