# Mass drug administration of ivermectin and dihydroartemisinin-piperaquine against malaria in settings with high coverage of standard control interventions: a cluster-randomised controlled trial in The Gambia

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# Summary

**Background** Although the malaria burden has substantially decreased in sub-Saharan Africa, progress has recently stalled. We tested whether mass administration of ivermectin, a mosquitocidal drug, with dihydroartemisinin-piperaquine, an antimalarial treatment, can reduce malaria in settings where coverage of standard control interventions is high.

**Methods** This cluster-randomised trial was carried out in 32 Gambian villages randomised (1:1) to either the intervention or the control groups. Three monthly rounds of mass drug administration with ivermectin and dihydroartemisinin- piperaquine per year were implemented in intervention villages over two malaria transmission seasons, in 2018 and 2019. Primary outcomes were malaria prevalence (all ages) at the end of the second year of the intervention, and *Anopheles gambiae s.l.* parous rate. The trial is registered with ClinicalTrials.gov, number NCT03576313.

**Findings** The total study population was 10638, with 46% (4939) in the 16 intervention villages. At the end of the second intervention year, malaria prevalence was 13% (324/2529) in the control group and 5% (140/2722) in the intervention group (odds ratio 0·30, 95% CI 0·16-0·59; p<0·0001). Incidence of clinical malaria was 1·10/100 person-months (348/31686) in the control group and 0·24/100 person-months (65/27460) in the intervention group (incidence rate ratio 0·21, 95% CI 0·10-0·43; p<0·0001). There was no difference in vector parity between study groups (p=0·537). Vector density was significantly lower in the intervention than in the control group (rate ratio 0·36, 95%CI 0·21-0·64; p<0·0001). Most adverse events were classified as mild and resolved in few days. No serious adverse events associated with the intervention were reported during the follow up.

**Interpretation** The intervention was safe and well-tolerated. Mass drug administration of ivermectin and dihydroartemisinin-piperaquine significantly reduced malaria prevalence and incidence in an area where coverage of standard control interventions is high.



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# Introduction

Between 2000 and 2015, the large scale-deployment of insecticide-treated nets (ITNs) and indoor residual spraying (IRS), with improvement in diagnosis and treatment resulted in a substantial decrease of malaria morbidity and mortality in sub-Sahara Africa.[1] Progress has recently stalled and many high burden countries are losing ground.[2] Two of the goals of the Global Technical Strategy 2016-2030[3] are off track as the reductions in morbidity and mortality achieved by 2020 are lower than expected [2].

In The Gambia, the malaria burden has substantially declined between 2010 and 2015.[4] Nevertheless, despite the high coverage of standard control interventions, malaria transmission persists in eastern Gambia while it has declined in all other regions. Between 2013 and 2014, incidence of clinical malaria was 1·7/person-year in eastern Gambia, while only 0·2/person-year in central Gambia and 0·1/person-year in western Gambia. [5]

There is a need for new interventions to further reduce and interrupt transmission.[6] Ivermectin is a broad-spectrum antiparasitic endectocidal drug able to kill mosquitoes feeding on treated humans.[7] If applied to a large proportion of the human population, it may reduce vector survival and consequently malaria transmission.[8] The duration of this effect is dose dependent, with high mosquito mortality up to 28 days after administering 300 µg/kg/day for 3 days.[9] Ivermectin is effective against insecticide-resistant mosquitoes,[7,10–12] and targets malaria vectors regardless of whether they bite indoors or outdoors.[13] Its safety profile is excellent as it has been used extensively for the control of lymphatic filariasis and onchocerciasis.[9,14,15]

Mass drug administration (MDA) with antimalarial drugs can have a pronounced effect on community parasite carriage but is prone to malaria resurgence, especially with sub-optimal coverage.[16] Dihydroartemisinin-piperaquine (DP) is one of the most attractive drugs for Intermittent Preventive Treatment or MDA. It is highly effective and the long half-life of piperaquine provides 1-2 weeks' longer post-treatment prophylaxis than other artemisinin-based combination therapies such as artemether-lumefantrine.[17] MDA with DP significantly reduced prevalence of infection and clinical malaria incidence in lower- but not in higher-transmission strata in Zambia.[18]

Adding ivermectin to the antimalarial treatment used for MDA may have an additive effect to standard vector control interventions; because of repeated biting, the likelihood that anophelines encounter a lethal dose is high, even if ivermectin coverage is incomplete.[13] Therefore, we assessed the impact of ivermectin plus dihydroartemisinin-piperaquine (DP) on both prevalence of falciparum

infection and survival of malaria vectors was assessed in an area of moderate malaria transmission and high coverage of ITNs and IRS in The Gambia.

# Methods

**Study design and participants**

This was a two-arm, open-label controlled cluster randomised trial carried out in Upper River Region (URR, 13°23'40"N 14°10'31"W), eastern Gambia, an area of highly seasonal malaria with peak transmission between September and November.[5] The main malaria vectors are *Anopheles arabiensis*, *A. gambiae s.s*. and *A. coluzzii.* URR has the highest vector parity rate in the country, varying between 77-91%, indicating high vector survival. [5,19]

Thirty-two villages with a baseline *Plasmodium falciparum* prevalence (all ages) by molecular methods ranging between 7-46% and separated from each other by at least 3 km to reduce the spill-over of vectors between villages, were selected from an earlier cross-sectional survey and randomised to either the intervention or the control group.[20] A buffer zone of 2 km radius was created around intervention villages to limit introduction of infections from neighbouring villages not included in the evaluation. Community sensitization meetings to provide information on the study and to answer any questions were held in all study villages. In intervention villages, additional meetings for optimal participation were held 2-5 days before implementing the intervention. The enumeration of the population in all study villages was carried out in November 2017. Written informed consent was obtained from all eligible residents willing to participate. Consent and enrolment procedures were carried out throughout the trial to include new residents and individuals absent at the time of the first consenting and enrolment procedures.

The trial protocol has been published elsewhere.[21] Ethical approval was obtained from The Gambia Government/MRC Joint Ethics Committee and the London School of Hygiene and Tropical Medicine Ethics Committee. The trial is registered with Clinical Trials.gov NCT 03576313.

**Randomisation and masking**

Villages were randomly allocated in 1:1 ratio to one of the two groups using a computer-based randomization performed by the trial statistician. Restricted randomisation, restriction that the baseline prevalence in one arm could not be more than 10% higher than the other, was used to ensure comparability between study groups. [22] Masking was not possible given the nature of the intervention; observer bias was reduced as laboratory staff were masked to the origin of the samples (clinical and entomological) they processed. Datasets were unmasked once data critical for the listed endpoints were locked.

**Procedures**

In all intervention villages, three monthly rounds of MDA with ivermectin (Laboratorio Elea, Argentina) and DP (Guilin Pharmaceuticals, China) were conducted each year over two malaria transmission seasons, in 2018 (August, September, and October) and 2019 (July, August, and September). DP was administered orally by body weight according to the manufacturer's instructions. Ivermectin was administered orally at the dose of 300-400 μg/kg/day for three consecutive days. Eligibility differed by treatment and was assessed at each MDA round. Inclusion criteria were: (1) age/anthropometry, for ivermectin: weight ≥15 kg; for DP: age >6 months, (2) willingness to comply with trial procedures, and (3) individual written informed consent. The exclusion criteria for both ivermectin and DP were known chronic illnesses such as HIV, tuberculosis, hepatitis, and severe malnutrition. Additionally, for ivermectin only, exclusion criteria were (1) pregnancy (any trimester) or breastfeeding, (2) hypersensitivity to ivermectin, and (3) travel to Loa loa endemic countries (Central Africa); for DP, these were: (1) first-trimester pregnancy, (2) hypersensitivity to DP, and (3) taking drugs that influence cardiac function or prolong QTc interval. Both control and intervention clusters received standard malaria control interventions conducted by the National Malaria Control Program (NMCP), namely ITNs, IRS with pirimiphos-methyl (Actellic 300CS), prompt diagnosis and treatment with artemether-lumefantrine, SMC with sulfadoxine-pyrimethamine plus amodiaquine, and intermittent preventive treatment during pregnancy (IPTp) with sulfadoxine-pyrimethamine.[21] In intervention villages, during the monthly MDA round, SMC was administered only to children aged 3-6 months as children >6-59 months old received DP. After the third MDA round and if SMC rounds were scheduled, 3-59 months children in intervention villages received SMC.

In each intervention village, daily treatment was administered under direct observation at a central location. Eligible individuals absent at the time of drug administration were followed up at home. Individuals' participation, demographic data and relevant medical history were electronically captured by tablet computers (Galaxy Tab 10.1 LTE Samsung Electronics, Korea). Eligible village residents in buffer zones were also treated with DP and ivermectin but not included in the evaluation of the intervention.

**Adverse events**

Information on adverse events occurring during the first 2 days of treatment was actively collected by the study team at the time of drug administration. Moreover, a structured questionnaire on adverse events, including their severity (mild, moderate, or severe), date of onset and duration, was administered to all treated individuals seven days after the first dose. The relation to the study drug was assessed based on known side-effects and timing to treatment. Any identified adverse event was

actively monitored until resolution. Throughout the study period, study participants were encouraged to inform the study team of any adverse events.

**Malaria prevalence and incidence**

Cross-sectional surveys to estimate malaria prevalence were carried out in November 2018 and November 2019, at the peak of the transmission season.[5] In each village, participants were randomly selected from the census list. A blood sample was collected by finger prick for dried blood spot. Malaria prevalence was estimated as the proportion of individuals positive for malaria infection diagnosed by molecular methods over the total number of individuals sampled. Passive detection of clinical malaria cases was established at both community and health facility level from July 2019, immediately after the first MDA round, until the end of December 2019, the end of the malaria transmission season. A rapid diagnostic test (RDT; SD BIOLINE Malaria Ag Pf Standard Diagnostics) was performed in all suspected cases (patients with fever and/or history of fever in the last 24 hours without any other likely cause than malaria) and positive individuals treated with artemether-lumefantrine. A blood sample for thick blood film and for later qPCR analysis (blood spot on Whatman 3 Corporation, Florham Park, USA) was collected from all RDT positive cases.

**Sample processing**.

*P. falciparum* was detected by quantitative polymerase chain reaction (qPCR) from the blood-spot samples. DNA was extracted from filter papers using an automated QIAxtractor robot (Qiagen) and tested for parasite prevalence by qPCR [23].

**Entomology**

In all villages, adult mosquitoes were collected indoors with CDC light traps. Seven to 14 days after each MDA round, intensive sampling for four consecutive nights was carried out in six randomly selected houses per village in 16 intervention and eight randomly selected control villages. Similar collections were carried out in the remaining control villages but only for one night. Subsequently, monthly collections were carried out in all villages for one night per month in six randomly selected houses per village, until the end of the transmission season (December). In addition, monthly human landing catches (indoor and outdoor) were carried out in three houses for two nights in four randomly selected villages per arm. Vector density was estimated with the CDC light traps, while for vector parity CDC light traps and human landing catches were combined. The direct insecticidal efficacy of ivermectin was evaluated by randomly selecting from one intervention village: 40 adults (≥18 years old) and 40 children (4-10 years old) who had taken, besides DP, the full ivermectin dose; the same number of individuals was selected from one control village. Blood samples (3 ml) were collected at

7-, 14- and 21-day post-intervention and fed to insectary-reared *A. gambiae* s.s. mosquitoes whose mortality was monitored daily until 14 days after feeding.

**Outcomes**

Primary outcomes measures were malaria prevalence by qPCR (all ages) at the end of the second intervention year, and *A. gambiae* s.l. parous rate, 7-14 days after MDA, determined by dissection.[24] Secondary outcomes were incidence of clinical malaria, mosquito mortality in membrane feeding assays, vector density, sporozoite rate, adverse events and intervention coverage.[21]

**Statistical analysis**

Sample size calculations were done for both primary outcome measures. For malaria prevalence, assuming an average prevalence of 15% and a coefficient of variation of 0.5, 16 villages per group and 200 individuals per village would be able to detect an effect size of 50%, i.e., from 15% to 7.5%, at 90% power and 5% significance level. For the vector parous rate, assuming the intervention would decrease parity from 85% to 75%, and a coefficient of variation of 0.25, dissecting 50 mosquitoes per village would have 90% power to find a significant difference between groups.

Analysis was done according to a pre-defined plan, finalised before the datasets were locked. Random effect logistic regression was used to compare the primary outcomes (malaria prevalence and vector parous rate) in the intention-to-treat-population between study groups; a random effect for study village (cluster) was included to take clustering into account. An analysis adjusting for age, ITN use, closed eaves, village baseline prevalence was also done. For the secondary outcomes, incidence of clinical malaria was compared between groups using random effects Poisson regression. Mosquito density (the number of mosquitoes collected per trap per night) was compared between groups using random effects negative binomial regression. Sporozoites rate was estimated on mosquitoes collected by CDC light traps. Sporozoites rate was compared between groups by random effect logistic regression. Entomological inoculation rate (EIR), the number of infective bites received per person during the transmission season, was estimated in each study group as 1.605 x (no. of positive Elisas/no. of catches) x 180.[25] The 95% CI for EIR were calculated assuming a negative binomial distribution for the mean number of *A. gambiae* s.l./light trap/night, to account for over-dispersion, and taking village as the unit of analysis. Survival time of laboratory-reared mosquitoes after feeding was analysed using Cox regression to calculate hazard ratios (HRs). We used shared frailty model with a gamma distribution to account for mosquitoes being from the same assay. Kaplan-Meier (K-M) plots were also presented summarising survival probability by treatment group over follow-up time. Coverage for each treatment was defined as the proportion of eligible individuals who received at

least one dose. The denominator for coverage in 2018 was the total eligible population at the beginning of the implementation while in 2019 it was the total eligible population at the beginning of each MDA round. Overall coverage was defined as the proportion of individuals who received at least one treatment dose divided by the total population (eligible and non-eligible). Adverse events were reported by MDA rounds. Analyses were performed with STATA version 15.

**Role of the funding source**

The funder of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author and the trial statisticians had full access to all the data in the study and the corresponding author had final responsibility for the decision to submit for publication.

# Results

The total study population was 10638, of which 4939 (46%) were in the 16 intervention villages (figure 1). At baseline, in November 2017, malaria prevalence was similar between study groups (table 1).

Implementation of the trial was substantially delayed in 2018 as both ethical and regulatory approvals took longer than expected. This resulted in the implementation of the first MDA round at the end of August (instead beginning of July) and in several other logistical challenges that affected coverage, including late arrival of study drugs, and limited time for communities' engagement. In 2018, coverage for the 4370 villagers eligible for DP was 2552 (58·4%), 2246 (51·4%), 2143 (49·0%) for rounds one, two and three, respectively. Coverage for the 3725 villagers eligible for ivermectin was 1946 (52·2%), 1747 (46·9%), 1771 (47·5%) for rounds one, two and three, respectively. Activities carried out in 2018 and the challenges mentioned above were critically reviewed by the study team and corrective actions taken, e.g. restructuring of the field team, including posting one research staff in each study village, adequate planning and time for community engagement. In 2019, the intervention was implemented as planned in July, August, and September, and coverage was substantially higher than the previous year. Coverage for DP was 86·0% (3991/4640) for the first round, 76·9% (3750/4875) for the second round and 76·1% (3752/4928) for the third round. Coverage for ivermectin was 82·9% (3156/3805), 72·4% (2952/4075) and 71·7% (2979/4155) for rounds one, two and three, respectively. Overall coverage for DP was between 51·4% and 58·4% in 2018 and between 76·0% and 85·5% in 2019; for ivermectin, overall coverage was between 40·0% and 44·5% in 2018 and between 60·3% and 65·5% in 2019 (appendixes 1A and 1B).

In November 2019, malaria prevalence, the primary outcome measure, was 13% (324/2529) in the control group and 5% (140/2722) in the intervention group (OR 0·30, 95%CI 0·16-0·59; p<0·001) (table

2). The effect was similar after adjusting for age, ITN use, closed eaves, travel outside the village and baseline prevalence (OR 0·28, 95%CI 0·14-0·56, p<0·001) (appendix 2). The range of cluster level prevalence in the intervention group was from 0% to 18% and 5% to 51% in the control group (appendix 3). In 2018, malaria prevalence was 14% (324/2252) in the control group and 11% (245/2166) in the intervention group (OR 0·63, 95%CI 0·36-1·10; p=0·107) (appendix 4). The range of cluster level prevalence in the intervention group was from 1% to 46% compared to 4% to 25% in the control group (appendix 3).

Clinical malaria incidence was not determined in 2018. Between July and December 2019, 413 clinical malaria episodes were reported (65 in the intervention and 348 in the control group). Incidence of clinical malaria was 1·10/100 person-months (348/31686) in the control group and 0·24/100 person-months (65/27460) in the intervention group (incidence rate ratio 0·21, 95% CI 0·10-0·43; p<0·0001), (table 2). The effect of the intervention was particularly marked between September and November (figure 2). There was some evidence of overdispersion in the Poisson model but fitting a negative binomial regression to account for overdispersion provided similar results albeit with slightly wider confidence intervals.

Although there was a tendency for a lower parity in the intervention group, both in 2018 and 2019, the difference was not statistically significant (p=0·322 and p=0·537 in 2018 and 2019, respectively) (table 3).

In 2018, 530 members of the *A. gambiae* complex were collected using CDC light traps, 151 (28·5%) from the intervention group. In 2019, 1780 *A. gambiae* s.l. mosquitoes were collected, 916 (51·5%) in the intervention group. Species composition was similar in both study groups (appendix 5).

In 2018, vector density tended to be lower in intervention group than in control group and was significantly lower in 2019 (RR 0·36, 95%CI 0·21-0·64; p<0·001) (table 3). Sporozoites rates were similar between the two study groups in both years (table 3). In 2018, EIR was similar between intervention and control villages. However, in 2019, EIR was significantly lower in intervention (3·00; 95%CI 1·76-5·14) than in control (11·7; 95%CI 6·72-16·91) villages (EIR ratio: 0·26, 95%CI 0·13-0·51; p<0·001) (table 3).

Mortality among mosquitoes fed on a blood sample taken at 7, 14 and 21 days after participants were treated with ivermectin was higher than in the control group, with the highest effect observed seven days post-treatment (Hazard ratio [HR] 2·5, 95%CI 2·17-2·87; p<0·01) (figure 3, appendices 6 and 7). In the Cox-regression model, the effect on mosquito's mortality remained significant up to 21 days post-treatment across all time-points (appendix 6). In a sub-group analysis, mosquito mortality was

more pronounced in individuals with body mass index (BMI) ≥ 22, with the greatest effect 14 days post-treatment (HR 6·32, 95% CI 4·04-10·08, p<0·0001) (appendix 6). HRs should be interpreted as the average effects overtime rather than constant effect at each time as the scaled Schoenfeld residuals showed some departure from the proportional hazards assumption, mainly reflecting declining treatment effect over time.

In 2019, AEs were recorded in 386 (9·7%) of 3991 participants in round 1, 201 (5·4%) of 3750 in round 2 and 168 (4·5%) of 3752 in round 3. Most AEs were classified as Grade 1 severity i.e. mild (table 4). All AEs resolved in a few days. Few cases of transient visual disturbance were reported (table 4). There were 11 serious adverse events (SAEs) (appendix 8), none of them related to the investigational products; three of them resulted in death, i.e., a road traffic accident with multiple injuries; a gastro-enteritis case secondary to HIV infection; and an undiagnosed illness. The latter occurred in a woman >70 years old who died at home after a short illness and without reporting to the health centre. She had received just one daily dose of MDA during the first round, in July 2019, and death occurred in September 2019.

# Discussion

MDA with ivermectin and DP reduced malaria prevalence, the primary parasitological endpoint, by about 60% and malaria incidence by about 80% but not vector parity, the primary entomological endpoint measuring vector survival. This could indicate that the observed difference in malaria prevalence and incidence between intervention and control groups may be essentially due to DP. Although there was no difference in mosquito population survival in both study groups, as shown by the similar parity between groups, the intervention resulted in lower vector density. Such decline was insufficient to reduce the overall vector survival rate, perhaps because of spill-over of vector populations from control villages mixing with those from intervention villages, as already observed in The Gambia.[26] This may have occurred despite the implementation of MDA in all villages located within 2 Km of each intervention village. Nonetheless, in 2019, when ivermectin coverage was above 70%, the impact of the intervention on vector density resulted in a 74% lower EIR in intervention villages, indicating decreased malaria transmission.

The vision of WHO and the global malaria community is a world free of malaria. All countries can accelerate efforts towards elimination through combinations of interventions tailored to local contexts.[3] However, currently available tools may not be sufficiently effective to interrupt malaria transmission.[27] One of the pillars of the current Global Technical Strategy is accelerating efforts towards elimination while research is one of the two supporting elements of this strategy.[3] The results of this trial fit within this context, particularly when considering that The Gambia has recently set the

goal of elimination by 2025.[28] Nevertheless, achieving such a goal may prove challenging with standard control tools since, despite high coverage, malaria transmission in the study area has not been interrupted. MDA with ivermectin and DP could provide an additional intervention towards the goal of elimination.

The current trial design is unable to determine the individual effect of each component of the MDA. The trial assessed the combined effect of DP and ivermectin as MDA because, at the time of designing the trial, MDA with ivermectin alone was considered unlikely to be implemented; combining DP, an efficacious antimalarial, with ivermectin, a mosquitocidal agent, would have a synergistic effect as the former would reduce the population parasite biomass and provide post-treatment prophylaxis while the latter would reduce vector densities and thus the number of infectious bites during and after the intervention.[7,29–31] Eventually, ivermectin would reduce the minimum coverage required by MDA as mosquitoes, by feeding on several individuals over a short period, may also take a toxic dose of ivermectin.

Recent mathematical models, however, predict that in highly seasonal transmission settings, such as our study site, ivermectin alone, either as a single dose of 400 µg/kg or 3 daily doses of 300 µg/kg implemented over 3 monthly rounds per season, would achieve a reduction of clinical incidence between 62% and 71%; by adding DP, the reduction would be between 91% and 94%.[13] The same model predicts that 3 monthly rounds of DP with ivermectin, the latter either as a single dose of 400 µg/kg or 3 daily doses of 300 µg/kg, would reduce malaria prevalence by 70% to 72%.[13] Notably, the model predicts that combining ivermectin with DP would prolong the overall effect of the MDA intervention. Our results are slightly lower than the model predictions, namely a reduction of 60% in malaria prevalence and 79% in clinical incidence, while the model predicts a reduction of 70% and 94%, respectively.

Our results differ from the two other cluster randomized controlled trial (CRCT) assessing MDA with DP alone carried out in sub-Saharan Africa. A reduction in the prevalence of infection and incidence of clinical malaria was observed in Zambia only in lower-transmission areas (prevalence <10%) while in Zanzibar the intervention had no effect on prevalence or incidence of clinical malaria.[18,32] In Zambia, malaria prevalence was determined by RDT and microscopy, and only in children below six years of age, while in Zanzibar this was by molecular methods and in all age groups. Therefore, in Zambia, prevalence in lower-transmission areas (between 7% and 9%) may be comparable to The Gambia had molecular methods been employed. Results in Zanzibar suggest that at baseline prevalence of 1.6%, MDA with DP or any other antimalarial may not be indicated.

In 2018, DP coverage was below 60% while ivermectin coverage was 50% or less, underlining the challenges to achieve the required 70-80% MDA coverage of the eligible population to reduce malaria transmission. Such less-than-optimal coverage was the result of poor community sensitization and involvement of the study population due to the delay in obtaining the required approvals and the little time available, given the short transmission season, for MDA implementation. One of the main barriers to non-participation and non-adherence in MDA is short-term mobility.[33] Villagers may not be available during the enumeration, consent process, or MDA rounds, requiring the setup, throughout the trial implementation, of a complex system ensuring these individuals are registered, provide written informed consent, and are followed up at home for treatment. Perceived adverse drug reactions, inconveniences related to the logistics of MDA (e.g., waiting times) and the perceived lack of information about MDA are additional factors that require careful planning for continuous sensitization meetings to provide accurate information on procedures, drug regimens and expected adverse drug reactions. High uptake of the intervention is key for the success of MDA campaigns.[34] This may be challenging if MDA becomes part of the standard interventions package. Nevertheless, the SMC coverage achieved where this is implemented, on average above 80%,[2] suggests that reaching the required MDA coverage may be feasible.[35] In addition, MDA should not be implemented for an indefinite number of years but for the time necessary to reduce malaria prevalence to extremely low level, e.g. 1-2%, when surveillance of clinical cases or other targeted interventions would be more adequate than MDA. This is also supported by the lack of impact of MDA in Zanzibar.[32] Restricting MDA to a limited number of years and ensuring good adherence to treatment would also decrease the risk of selecting drug resistance parasites. Moreover, to decrease the risk of selecting drug resistance parasites, we purposely choose for MDA a different antimalarial treatment than the first line treatment, which is artemether-lumefantrine in The Gambia.

In 2018, despite sub-optimal coverage, malaria prevalence tended to be lower in the intervention group than the control group. This result was heavily influenced by the prevalence in children <5 years of age, which was 2-fold higher in intervention than control villages. In 2019, with an MDA coverage above 70%, prevalence across all age groups was >60% lower in intervention than in control villages.

In 2019, clinical incidence was about 80% lower in intervention than control villages. However, incidence rate in children below 5 years were similar in intervention and control villages. This was probably due to high coverage of SMC, which was implemented monthly in all study villages (intervention and control) from July to October 2019.

Sporozoite rates were also similar between study groups, which is surprising given the high DP coverage and the lower prevalence in the intervention group. This finding provides further support for mixing of the vector population between intervention and control villages. Although the sporozoite rates were comparable between study groups, there were far fewer *A. gambiae* s.l. in the intervention villages in 2019, resulting in >70% lower EIR than in control villages. Our results suggest that using MDA with ivermectin over a much larger area, to reduce invasion of mosquitoes from untreated villages, could reduce vector population survival, resulting in even greater reductions in the EIR. *A. arabiensis* was the most abundant species in the study site, representing more than half of the malaria mosquitoes collected in 2018 and more than two-thirds in 2019. Given this species also feeds readily on animals, this may have diluted the impact of ivermectin on vector survival and suggests that ivermectin administered to both humans and cattle may provide improved mosquito killing. Nonetheless, treating cattle with ivermectin boluses may have the undesirable consequences of killing dung beetles, reducing biodiversity, impacting the soil-nutrient cycle and ecosystem functioning.[36]

Mosquito survival was reduced by about 60% after 7 days post treatment and by about 30% after 21 days post-treatment, indicating a robust and prolonged mosquitocidal effect, and confirming earlier results from Kenya and Thailand. [9,30] Adding DP to ivermectin increases the peak concentration and overall exposure to ivermectin, resulting in higher toxicity to mosquitoes and a prolonged effect because of the slow-release of ivermectin metabolites.[30] The mosquitocidal effect is markedly pronounced with higher BMI as mosquito mortality increased significantly when fed on blood of participants with a body mass index ≥ 22. This phenomenon has already been described and may be due to the accumulation of ivermectin in fat tissue which would then be slowly released, increasing its blood concentration over time and thus the mosquitocidal effect.[9]

Overall, the intervention was safe and well tolerated, confirming the high safety profile of repeated and high dose of ivermectin co-administered with DP. [9,15] Most AE were mild; few individuals had transient visual disturbances that resolved in a few hours. Nevertheless, no systematic monitoring of biochemistry parameters was carried out nor an electrocardiogram (ECG) performed. This would have been important to detect any liver or renal injury or any QTc (QT interval corrected for heart rate) prolongation when considering the co-administration of DP and ivermectin can result in higher concentration of ivermectin and piperaquine. [30]

There are some limitations to our study. First, the study communities could not be blinded to the intervention. Second, we did not achieve the sample size required for measuring parity in both study groups. Third, although the villages were separated by distances of 3 km and MDA the was

implemented in all villages within 2 km of each intervention village, there may have been spill-over between adjacent villages.

This is the first study to show that community administration of three-monthly MDA of DP and high dose ivermectin is safe and well-tolerated and reduces residual malaria transmission in an area of highly seasonal malaria with high coverage of control interventions. Adding MDA with ivermectin and DP to the currently available malaria control interventions could further reduce malaria transmission and possibly accelerate malaria elimination in areas with high coverage of vector control interventions.

**Contributors**

UDA conceived the study. EDD, HMS, FC, JB, BK, MRS, HS, KPG, HB, TB, CD, SWL, JA and UDA contributed to refinement of the protocol and approved the final version. JB was the trial statisticians. EDD, HMS, UDA and NM contributed to data analysis. EDD, HMS, BC, FC, and MON did the field work and data collection. EDD and UDA drafted the manuscript. All authors read and approved the final manuscript before submission.

**Declaration of interests**

We declare no competing interests.

**Data sharing**

After publication, trial data will be made available on reasonable request to the corresponding author. A proposal with a detailed description of study objectives and a statistical analysis plan will be needed for assessment of requests. Additional materials might also be required during the process of assessment. Deidentified participant data will be provided after approval by the sponsor and trial management group.

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Table 1: Baseline characteristics of the study population in November 2017

| | Control group | Intervention group |
|---|---|---|
| Number of villages | 16 | 16 |
| Population | 5699/10638 (54%) | 4939/10638 (46%) |
| | Baseline malariometric survey | |
| Females | 699/1217 (57 %) | 828/1430 (58 %) |
| Males | 518/1217 (43%) | 620/1430 (42%) |
| Age (years) | 13 (6,30) | 13 (6,31) |
| Age < 5 years | 198/1200 (16%) | 216/1420 (15%) |
| Age 5-14 years | 458/1200 (38%) | 541/1420 (38%) |
| Age > 14 years | 544/1200 (45%) | 663/1420 (46%) |
| ITN use previous night | 1023/1204 (85%) | 1233/1418 (87%) |
| Malaria prevalence | 211/1165 (18%) | 224/1392 (16%) |

Data are n/N (%) or median (IQR). IQR = interquartile range, ITN = insecticide treated nets

Table 2: Malaria prevalence and incidence by study arm, and age group in 2019

| **Malaria prevalence** | | | | |
|---|---|---|---|---|
| Age group (years) | Control group (n=2529) | Intervention group (n=2722) | OR (95% CI) | p-value |
| < 5 | 56/511 (11·0 %) | 19/477 (4·0 %) | 0·35 (0·13, 0·93) | 0·03 |
| 5-14 | 109/883 (12·3 %) | 46/948 (4·9 %) | 0·31 (0·14, 0·69) | 0·01 |
| ≥15 | 159/1130 (14·1 %) | 72/1200 (6·0 %) | 0·34 (0·18, 0·64) | 0·001 |
| All ages | 324/2529 (12·8 %) | 140/2722 (5·1%) | 0·30 (0·16, 0·59) | <0·0001 |

| **Incidence clinical malaria** | | | | |
|---|---|---|---|---|
| Age group (years) | Control group (IR) | Intervention group (IR) | IRR (95%CI) | p-value |
| < 5 | 0·32 (18/5700) | 0·20 (10/4940) | 0·58 (0·18, 1·88) | 0·360 |
| 5-14 | 1·37 (144/10507) | 0·30 (27/9106) | 0·22 (0·09, 0·54) | 0·001 |
| ≥ 15 | 0·98 (151/15481) | 0·19 (25/13417) | 0·18 (0·09, 0·38) | <0·0001 |
| All ages | 1·10 (348/31686) | 0·24 (65/27460) | 0·21 (0·10, 0·43) | <0·0001 |

Data are n/N, rates (event/person/month). OR=odds ratio, IR= incidence rate: case/person-month, IRR = Incidence Rate ratio

Table 3: Vector parity, sporozoite rate, entomological inoculation rate and vector density by study arm and year

| | 2018 | | | | 2019 | | | |
|---|---|---|---|---|---|---|---|---|
| Vector parity | Control group | Intervention group | OR (95% CI) | p-value | Control group | Intervention group | OR (95% CI) | p-value |
| MDA 1 | 297/518 (57·3 %) | 190/364 (52·2 %) | 0·98 (0·52, 1·87) | 0·951 | 131/186 (70·4%) | 72/94 (76·6 %) | 1·37 (0·77, 2·42) | 0·284 |
| MDA 2 | 442/634 (69·7 %) | 262/391 (67·0 %) | 1·00 (0·58, 1·71) | 0·987 | 81/105 (77·1%) | 107/155 (69·0 %) | 0·78 (0·43, 1·41) | 0·405 |
| MDA 3 | 130/157 (82·8 %) | 52/80 (65·0 %) | 0·31 (0·16, 0·61) | <0·001 | 238/259 (91·9%) | 229/252 (90·9%) | 0·87 (0·47, 1·62) | 0·661 |
| Survey 1 | 30/41 (73·2 %) | 17/20 (85·0 %) | 1·75 (0·23, 13·47) | 0·591 | 83/95 (87·4%) | 28/32 (87·5 %) | 0·59 (0·14, 2·46) | 0·469 |
| Survey 2 | 1/2 (50·0 %) | 0/0 (· %) | -- | -- | 19/19 (100v0%) | 5/7 (71·4 %) | -- | -- |
| Overall | 900/1352 (66·6%) | 521/855 (60·9%) | 0·85 (0·62, 1·17) | 0·322 | 552/664 (83·1%) | 441/540 (81·7%) | 0·90 (0·66, 1·25) | 0·537 |
| Vector density (CDC-LTC) | 1·6 (1572/1002) | 0·7 (562/858) | 0·49 (0··9, 1.29) | 0·150 | 3·4 (3088/912) | 1·4 (1914/1344) | 0·36 (0·21, 0·64) | <0·0001 |
| Sporozoite rate (CDC-LTC) | 2/456 (0·4%) | 4/202 (2·0%) | 4·58 (0·83, 25·24) | 0·080 | 37/3047 (1·2%) | 14/1902 (0·7%) | 0·60 (0·32, 1·12) | 0·109 |
| EIR (95% CI) | 0·58 (0·08, 3·86) | 1·35 (0·61, 8·68) | 2·34* (0·41,42·42) | 0·23 | 11·7 (6·72, 16·91) | 3·00 (1·76, 5·14) | 0·26* (0·13, 0·51) | <0·001 |

Data are n/N (%) OR=Odds ratio, CDC-LTC = light traps, EIR= entomological inoculation rate, *EIR ratio (95% CI)

Table 4: Reported adverse events and severity in 2019

| Adverse event | MDA 1<br>N=3991 | MDA 2<br>N=3750 | MDA 3<br>N=3752 |
|---|---|---|---|
| Headache | 82 (2·0) | 53 (1·4) | 46 (1·2) |
| Diarrhoea | 49 (1·2) | 16 (0·4) | 15 (0·4) |
| Vomiting/Nausea | 40 (1) | 11 (0·3) | 7 (0·2) |
| Abdominal Pain | 34 (0·9) | 20 (0·5) | 12 (0·3) |
| Pyrexia | 34 (0·9) | 25 (0·7) | 29 (0·8) |
| General Body Pain/Join pain | 32 (0·8) | 22 (0·6) | 8 (0·2) |
| Malaise | 18 (0·5) | 1 (0·03) | 8 (0·2) |
| Cough | 10 (0·3) | 6 (0·2) | 12 (0·3) |
| Transient visual disturbances | 7 (0·2) | 11 (0·3) | 15 (0·4) |
| Itching | 4 (0·1) | 1 (0·03) | 0 (0·0) |
| Other | 76 (2) | 29 (0·8) | 16 (0·4) |
| Grading (Severity)* | | | |
| Grade 1 (mild) | 333 (86·3) | 157 (78·1) | 153 (91·1) |
| Grade 2 (moderate) | 40 (10·4) | 35 (17·4) | 13 (7·7) |
| Grade 3 (severe) | 5 (1·3) | 3 (1·5) | 1 (0·6) |
| Grade not recorded | 8 (2·0) | 6 (3·0) | 1 (0·6) |
| Total | 386 (100) | 201 (100) | 168 (100) |

Data are n/N (%), * Grading (severity) of the adverse events over the total number of events recorded.