Safety of mass drug coadministration with ivermectin, diethylcarbamazine, albendazole, and azithromycin for the integrated treatment of neglected tropical diseases: a cluster randomized community trial

Lucy N John,[a,b,c,d] Camila Gonzalez-Beiras,[c] Marti Vall-Mayans,[c] Reman Kolmau,[e] Wendy Houinei,[a] James Wangi,[f] Michael Marks,[g,h,i,†] and Oriol Mitja,[c,d,e,†]*

[a]National Department of Health — Aopi Centre, Port Moresby, Papua New Guinea
[b]Barcelona Institute for Global Health - Faculty of Medicine, University of Barcelona, Barcelona, Spain
[c]Fight AIDS and Infectious Diseases Foundation, Hospital Germans Trias Pujol, Badalona, Catalonia (Spain)
[d]School of Medicine and Health Sciences, University of Papua New Guinea, Port Moresby, Papua New Guinea
[e]Lihir Medical Centre, International SOS, Lihir Island, Papua New Guinea
[f]WHO PNG Office — Aopi Centre, Port Moresby, Papua New Guinea
[g]London School of Hygiene and Tropical Medicine, London, United Kingdom
[h]Hospital for Tropical Diseases, London, United Kingdom
[i]Division of Infection and Immunity, University College London, London, United Kingdom

Summary

Introduction Neglected tropical diseases control programmes run separately. For settings with more than one endemic disease, combined mass drug administration (MDA) has potential practical advantages compared with separate programmes but needs confirmation of safety. We assessed the safety of combined MDA for multiple neglected tropical diseases using ivermectin, diethylcarbamazine, albendazole (IDA) and azithromycin (AZI).

Methods We conducted an open-label, cluster-randomized trial involving individuals living in 34 wards (smaller administrative division) in two study sites, Namatanai District and Lihir Island, Papua New Guinea. We randomly assigned wards to the combined treatment arm (which received a single dose of the triple combination IDA and a single dose of AZI at the same visit) or the control arm (which received IDA separately followed by AZI separately one week after). All participants underwent safety assessments one day after drug administration. Methodology for collecting the adverse events (AEs) was a general question (in Namatanai) and individual questions about specific AEs (in Lihir). The primary endpoint was the prevalence of AEs. Safety of combined treatment was taken to be non-inferior to that of IDA if the upper limit of the two-sided CI for the difference in rates was equal or lower than 5%.

Findings The study enrolled 15,656 participants. Of those enrolled, 7,281 (46.3%) received the combined regimen and 8,375 (53.3%) received standard treatment with IDA for lymphatic filariasis between Nov 1, 2018, and Apr 15, 2019. Of the individuals in the control group, 4,228 (50.5%) attended a second visit one week apart to receive AZI for yaws. In Namatanai, the proportion of AEs was similar in the combined group (0.8%) compared to the IDA group (1.3%, difference 0.5% [95CI -2.5% to 1.4%]) or the AZI group (3.6%, d -2.8% [95CI -8.6% to 2.8%]). In Lihir, the proportion of AEs was higher in the combined group (23.0%) compared to the IDA group (12.2%, d 10.8% [95% CI 1.5% to 20.2%]) or the AZI group (11.1%, d 11.9% [95% CI 2.7% to 21.1%]).We observed 21 (0.3%) grade-2 AEs in the combined treatment group, 33 (0.4%) in the IDA separately group, and 18 (0.2%) in the AZI separately group. No participants required treatment for any AE. We observed no deaths, serious AEs, or AEs of special interest.

Interpretation In the largest trial so far involving coadministration of regimens based on IDA and AZI, the combination was safe and feasible in a population of more than 15,000 people. Combined MDA based on these two regimens opens up new potential for the control of neglected tropical diseases in the Western Pacific region.

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*Corresponding Author. Dr Lucy Ninmongo John, National Department of Health, Papua New Guinea, +675 301 3736 or 72396952
E-mail addresses: lucyninmongojohn@gmail.com, lucy_john@health.gov.pg (L.N. John).
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† Joint Senior Authors

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Research in context

Evidence before this study

On Feb 15, 2021, we searched PubMed without language restrictions for articles containing the terms "mass drug administration", "ivermectin", "diethylcarbamazine", "albendazole", and "azithromycin" either in the title or the abstract. The search returned only two items: one review analysing literature of these treatments separately, and our previous pharmacokinetic study assessing the quadruple combination. We found no evidence on the administration of the quadruple combination in the field.

Added value of this study

Our trial was designed to investigate the safety of mass drug administration (MDA) of two integrated therapies with ivermectin, diethylcarbamazine, and albendazole (IDA) and azithromycin. To our knowledge, it is the first published large-scale trial of coadministration of this strategy to control neglected tropical diseases, providing safety information on more than 15,000 people. In our study, safety was evaluated using active monitoring of adverse events.

Implications of all the available evidence

IDA-based MDA is recommended in countries endemic for lymphatic filariasis outside sub-Saharan Africa, while both trachoma and yaws elimination programmes are based on MDA with azithromycin. Our study provides evidence that coadministration of IDA and azithromycin is feasible and safe in a neglected tropical diseases co-endemic setting. Our findings, therefore, encourage the strategy of integration of MDA for neglected tropical diseases sharing similar target populations and therapies to reduce costs and allow a more rapid scale-up of programmes.

Introduction

Mass drug administration (MDA) is the mainstay of control programs for many neglected tropical diseases (NTDs), including lymphatic filariasis, soil-transmitted helminths, trachoma, and yaws.[1–3] In most countries, NTD control programs typically run separately and deliver separate MDA campaigns for each targeted disease. Integration of activities has been highlighted as a priority in the World Health Organization Roadmap for NTDs.[4] MDA campaigns are one area where integration may reduce economic and logistic costs and potentially reduce complexity.[5]

Papua New Guinea is endemic for a number of NTDs targeted for elimination or eradication through MDA, including lymphatic filariasis, soil transmitted helminths (STH), trachoma, yaws, and scabies.[6–8] For the last 20 years, the main strategy for lymphatic filariasis elimination has consisted of repeated rounds of MDA with albendazole and either diethylcarbamazine or ivermectin. However, recent studies have shown that single-dose combination therapy with all three drugs—ivermectin, diethylcarbamazine, and albendazole (IDA)—is superior to the previous two-drug combinations, and may help accelerate lymphatic filariasis elimination.[1] In light of the emerging data on both, safety and efficacy of the triple combination, the WHO has provided alternative guidelines recommending IDA-based MDA in countries endemic for lymphatic filariasis outside sub-Saharan Africa.[9] IDA-based MDA for lymphatic filariasis is also likely to reduce the prevalence of both STH and scabies.[10,11]

Public health programmes for both trachoma, caused by serovars A, B, and C of *Chlamydia trachomatis,* and yaws, caused by *Treponema pallidum* subsp. *pertenue,* are based on MDA with the macrolide antibiotic azithromycin (AZI).[2,3]

Programmatic adoption of integrated MDA requires both pharmacokinetic data on any drug interactions and field studies evaluating the safety of integrated MDA. We recently reported the results of a clinical study that compared the pharmacokinetics of administration of IDA separately (lymphatic filariasis regimen) or AZI separately (yaws regimen) with coadministration of IDA and AZI (combined treatment regimen). Compared to separately administered treatment, the study demonstrated an absence of clinically relevant drug-drug interactions, and no severe adverse events (AE) were observed.[12] These findings paved the way for more extensive field studies to evaluate the safety of integrated MDA. In this study, we aimed to assess the safety of a large-scale administration of the combined treatment regimen for lymphatic filariasis and yaws.

Methods

Study setting and participants

We conducted a cluster-randomized controlled trial in four local level government (LLG) areas in the New Ireland Province in Papua New Guinea (PNG): three in

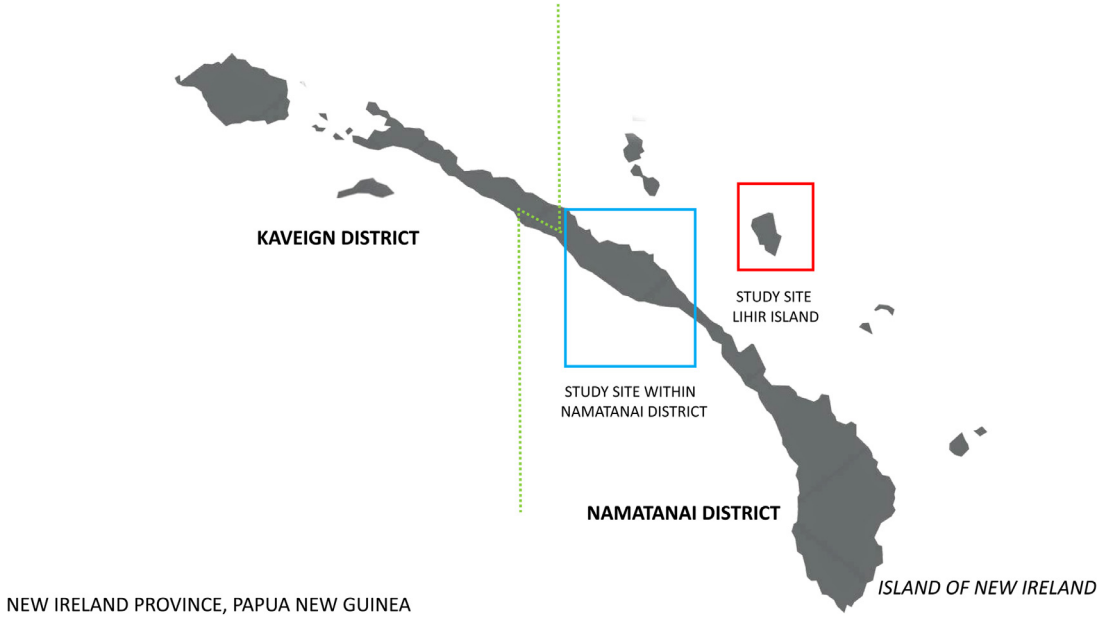

Figure 1. Study Map

the Namatanai District in the island of New Ireland (Matalai Rural LLG, Namatanai Rural LLG, and Sentral Niu Ailan Rural LLG), and one in the Lihir Island (Nimamar Rural LLG) (Figure 1). Clusters were individuals living in the same ward, which is the smaller administrative unit in PNG. A ward consists of 500-1,000 persons living in a group of neighbouring villages that generally share a school or church. Each LLG in the study area has between 7-21 wards that are identified with consecutive numbers. We randomized 34 wards (19 in Namatanai and 15 in Lihir) to either an experimental arm or a control arm. The intervention first started in Namatanai District alongside two public health campaigns: a trial designed to assess the effectiveness of an MDA strategy to eliminate yaws at the population level (NCT 03490123); and an MDA round with IDA, launched by the National Department of Health for the elimination of lymphatic filariasis. Due to a lower-than-expected enrolment in Namatanai, the study was expanded to Lihir Island alongside the ongoing rollout of IDA by the National Department of Health. The study was conducted in November 2018 (Namatanai) and April 2019 (Lihir).

All individuals older than 6 months and living in the study area were eligible to participate. Contraindications for individual drugs were in line with PNG National Department of Health guidelines for MDA, which include concomitant use of medications contraindicated with any MDA drug, and pregnancy (verbally declared) or breastfeeding. Participants who were unable to take oral medication and those who did not give informed consent or who withdrew consent were also excluded. Supplementary file 1 provides a detailed list of exclusion criteria. The study was approved by Medical Research Advisory Committee of Papua New Guinea (MRAC 17.19). The ethics committee approved the use of oral consent.

Randomization and interventions

Randomization was performed at the level of the ward and stratified by study site (i.e., Namatanai and Lihir). A randomisation sequence was generated using R and a block size of 4. Wards were randomized to receive one of two treatment regimens: in the experimental arm, villages received a single visit at which time a combined MDA for lymphatic filariasis and yaws were conducted consisting of IDA and AZI at the same time. In the control arm, villages received an initial visit at which time MDA for lymphatic filariasis was conducted with IDA, and then one week later a second visit when MDA for yaws was conducted with AZI. All drugs were administered orally at standard dosing according to age (Table S1, Supplementary File 1) and in line with the WHO guidelines of MDA for lymphatic filariasis and yaws, respectively. All treatment was directly observed. AZI was provided free of charge by Kern Pharma Spain; ivermectin, diethylcarbamazine, and albendazole were donated through WHO to the National Department of Health of Papua New Guinea. Blinding of trial participants and outcome assessors was not possible as the intervention was embedded within programmatic MDA.

Study oversight

The field teams consisted of one community health worker (CHW) and 4 village health volunteers, all

supervised by the study research team, which consisted of three senior researchers. CHWs were given mobile phones for regular communication with the research team. All study personnel received training on data collection and AE reporting in both study islands.

Field teams visited candidate villages and met community leaders to explain the study purpose and procedures. Before any procedure, adult participants—parents, or guardians for participants younger than 18 years—provided verbal consent to participate. Individuals who consented to receive the regimen and enter the study were asked to attend the village clinic or community hall to receive treatment on an agreed date. Study drugs were delivered by field teams as part of the National Department of Health lymphatic filariasis program; in villages allocated in the control arm, an additional visit was scheduled one week after to deliver the dose of the AZI regimen for yaws.

Outcomes

The primary safety endpoint was the prevalence of self-reported AEs, defined as the proportion of participants who experienced at least one treatment-related AE following drug administration. Other endpoints included the occurrence of any serious AE (i.e., grade 3-to-4 toxicity). The onset of AEs was assessed by active surveillance using individual structured interviews conducted in Tok Pisin by field teams who remained in the villages for 24 hours after drug administration.

In Namatanai, field teams assessed the occurrence of AEs by asking an open-ended question ("Since the last visit, have you experienced any medical problem?") as part of the routine follow-up. Participants who answered in the positive were asked to identify the type of condition from a standardized list. Following enrolment in Namatanai, we noted a relatively low proportion of individuals reporting AEs across the whole study population. Therefore, when we expanded the study to Lihir, we switched to explicitly asking participants about each symptom individually. Answers in the positive in any of the questionnaire items were recorded in a clinical report form as an AE.

Regardless of methodology, for all AEs identified, the field teams gathered information regarding duration (i.e., start and end date), relationship with study drugs, severity, action taken, and outcome. AE severity was graded on a 1-4 scale using the GRADE system established in the Common Terminology Criteria for Adverse Events version 4.0. Participants with grade ≥2 AEs were examined by a study clinician. Whenever possible if appropriate, additional diagnostic testing and/or treatments could be provided free of charge to participants. Causality was graded using the following categories: related, not related, and not assessable. For the primary endpoint analysis, we included all AEs graded as "related" in the causality assessment. The study was registered on clinical trials.gov (NCT03676140).

Statistical Analysis

This study was based on the hypothesis that combined treatment would be non-inferior to separate MDA for the primary safety endpoint, according to a prespecified non-inferiority margin: the upper limit of the 95% confidence interval (CI) for the difference in AE rates would not exceed 5%. We compared combination MDA to both IDA and AZI separately. We originally calculated that 32 clusters of 450 individuals (sample size of 14,400 - 7,200 per group) would give a power of 80% to test the hypothesis of non-inferiority, assuming that 10% of participants would be lost to follow-up. This sample size accounted for an expected non-serious AEs rate of IDA of 10%, a non-inferiority margin of 5%, a one-sided type 1 error rate of 0.05, and a kappa value of 0.35. In addition, our large sample size provides power to detect rare AEs which might not be detected in smaller studies. As enrolment was lower than anticipated, we expanded the study to enrol additional clusters in Lihir.

The primary analysis was a per-protocol analysis which included all individuals who received the planned dose of the assigned drug, either IDA separately or AZI separately compared to combined treatment (i.e., coadministration of IDA and AZI), and responded to the AE questionnaire. Based on the existing safety profile of the drugs we assumed that nearly all adverse events would occur within a 24hr window following MDA. We therefore opted to consider each AE following each MDA separately. We calculated the proportion of individuals who experienced an AE after combined MDA, in the intervention arm, and for the proportion of individuals who experienced an AE after either the initial MDA (for lymphatic filariasis) or the second MDA (for yaws) in the control arm.

The frequency of AEs was described as the number of participants experiencing an AE and the percentage. Robust standard errors were used to adjust for clustering. We fitted a random-effects regression model which adjusted for clustering at the level of the ward to assess whether treatment arm was associated with the risk of experiencing an AE. Initially we had planned to conduct a single analysis combining data across the two sites. However, as the methods for eliciting AEs differed and this appeared to be associated with markedly different rates of reporting of AEs across the study sites we opted post-hoc to present analyses for the Namatanai and Lihir settings separately. Overall results are included in the Supplementary appendix.

The prevalence of participants with AEs, AEs grade, and "related" causality were calculated with the 95% CI and presented in the table format, grouped according to treatment: combined MDA with IDA and AZI, IDA separately, and AZI separately. We calculated an exact binomial CI to estimate the proportion of grade 3-4 NIH-NCI toxicity.

Role of the funding source

The funders had no role in the study design, data collection, data analysis or interpretation of data, or in writing

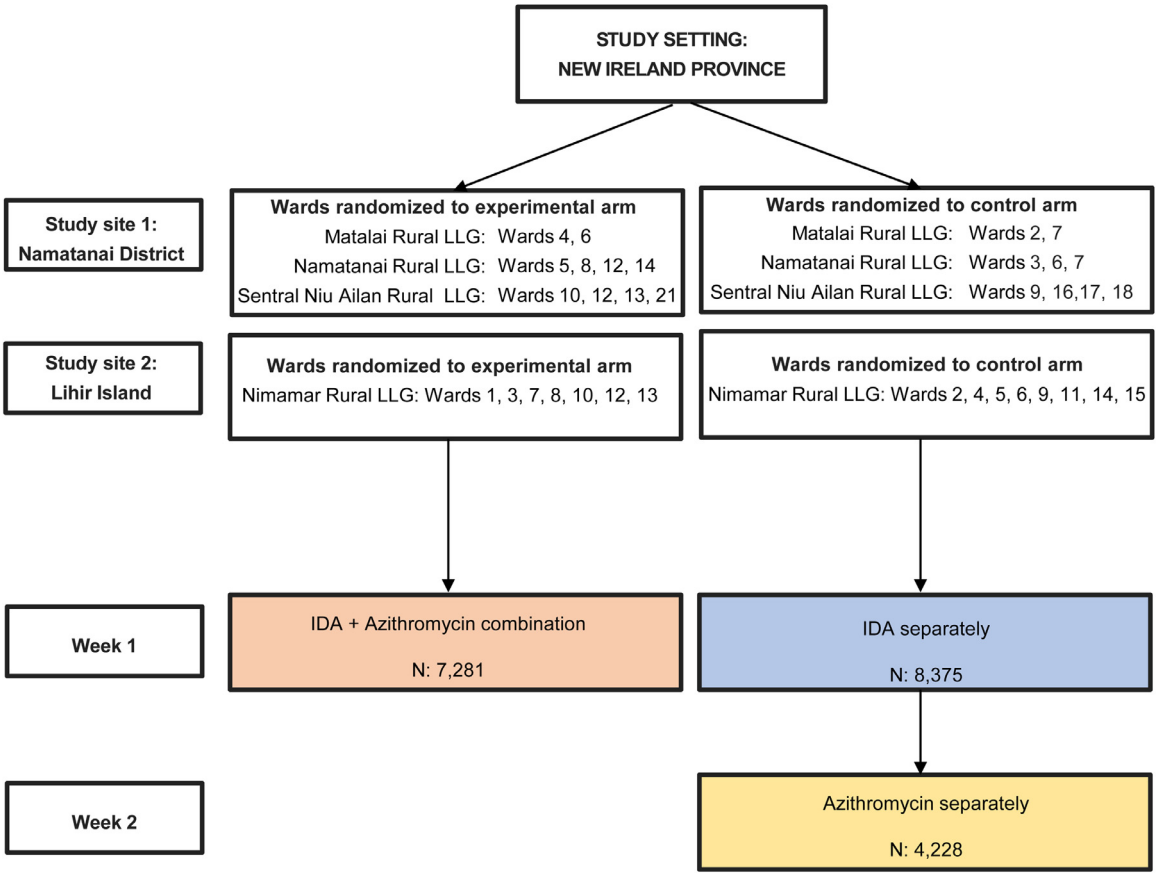

Figure 2. Trial profile

The study area consisted of three Local Level Government (LLG) areas in Namatanai District and one LLG in Lihir Island. We selected wards that were eligible to receive both yaws and LF MDA: 4 wards out of 7 in Matalai Rural LLG, 7 wards out of 15 in Namatanai Rural LLG, 8 wards out of 21 in Sentral Niu Ailan LLG, and all 15 wards in Nimamar LLG.

IDA: ivermectin, diethylcarbamazine, and albendazole. **MDA:** mass drug administration.

of the manuscript or decision to submit for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to publish.

Results

Between Nov 1, 2018, and Apr 15, 2019, 15,656 individuals from 34 wards met the inclusion criteria and provided verbal informed consent to participate in the study: 5,794 in Lihir, and 10,378 in Namatanai. Of them, 7,281 (46.3%) lived in wards allocated to the experimental arm and received the combined MDA with IDA plus AZI, and 8,375 (53.3%) lived in wards allocated to the control arm and started standard MDA with IDA for lymphatic filariasis (Figure 2). Of the individuals in the control arm, 4,228 (50.5%) attended a second visit one week apart to receive AZI. Table 1 summarizes the main characteristics of study participants and their distribution across treatment groups and settings.

In Lihir, the primary outcome was observed in 461 (23.0%) of 2,003 participants in the combined treatment group, 462 (12.2%) of 3,796 participants in the IDA group (absolute difference 10.8% [95% CI 1.5% to 20.2%]) and 389 (11.1%) of 3,496 participants in the AZI group (absolute difference 11.9% [95% CI 2.7% to 21.1%]). In Lihir, therefore, the non-inferiority criterion was not met for the primary safety outcome at 24 hours after combined drug administration compared to either IDA or AZI separately (Table 2).

In Namatanai, the primary outcome was observed in 42 (0.8%) of 5,278 participants in the combined treatment group, 62 (1.3%) of 4,650 participants in the IDA group (absolute difference -0.5% [95% CI -2.5% to 1.4%]) and 26 (3.6%) of 732 participants in the AZI group (absolute difference -2.8% [95% CI -8.6% to 2.8%]). In Namatanai, therefore, the non-inferiority criterion was met for the primary safety outcome at 24 hours after combined drug administration compared to IDA separately (Table 2).

	Combination MDA[a] N=7,281	IDA N=8,375	Azithromycin N=4,228
Male	3,465 (47.6%)	4,364 (52.1%)	2,107 (49.8%)
Female	3,816 (52.4%)	4,011 (47.9%)	2,121 (50.2%)
Age	18 (8-34)	18 (9-33)	18 (9-31)
Study site			
Lihir	2,003 (27.5%)	3,791 (45.3%)	3,496 (82.7%)
Namatanai	5,728 (78.7%)	4,584 (54.7%)	732 (17.3%)

***Table 1*: Participant characteristics at baseline**
IDA: ivermectin, diethylcarbamazine, and albendazole. **MDA:** mass drug administration.
[a] Coadministration of IDA and azithromycin.

In a random-effects regression analysis comparing combined treatment with IDA separately, older age and female gender were associated with an increased likelihood of reporting an AE (Table 3). When comparing combined therapy with AZI separately we also found an association with female gender, but not age, on the likelihood of reporting an AE.

Table 4 summarizes the frequency and type of AEs associated with each treatment regimen. Fatigue was the AEs most frequently reported after combined treatment (298/7,281; 4.1%) and IDA (248/8,441; 3.0%), whereas abdominal pain was the leading AE associated with AZI (191/4,228; 4.6%). The percentage of individuals reporting AEs in each cluster ranged from 0 to 60% (mean 12%; SD 14%).

AEs reported in the study were mostly Grade 1 and self-limiting. We observed 21 (0.29%) Grade-2 AEs in the combined treatment group, 33 (0.39%) in the IDA separately group, and 18 (0.21%) in the AZI separately group (Table S2). No participants required treatment for any AE. We observed no deaths, serious AEs, or AEs of special interest.

Discussion

In this cluster-randomized trial we found markedly different AE rates across our two study sites. In Namatanai coadministration appeared to meet the non-inferiority margin but in Lihir the rate of AEs was higher in the experimental arm and did not meet the prespecified non-inferiority margin compared with standard IDA separately. This reflects both the different methods used for eliciting AEs across study sites and the lower than the anticipated sample size. Whilst, in Lihir,

	Combination MDA[a]	IDA	Azithromycin	Difference between IDA and combined treatment (95% CI)	Difference between AZI and combined treatment (95% CI)
Lihir	**N=2,003**	**N=3,796**	**N=3,496**		
Participants reporting an adverse event, n (%)	461 (23.0%)	462 (12.2%)	389 (11.1%)	10.8% (1.5 to 20.2%)	11.9% (2.7 to 21.1%)
Namatanai	**N=5,278**	**N=4,650**	**N=732**		
Participants reporting an adverse event, n (%)	42 (0.8%)	62 (1.3%)	26 (3.6%)	-0.5% (-2.5% to 1.4%)	-2.8% (-8.6% to 2.8%)

***Table 2*: Trial outcomes**
CI: confidence interval. **IDA**: ivermectin, diethylcarbamazine, and albendazole. **MDA**: mass drug administration. **AZI**: azithromycin.
[a] Coadministration of IDA and azithromycin.

	Combination MDA vs IDA	*p* value	Combination MDA vs Azithromycin	*p* value
By Study Site				
Lihir				
Age (by 5-year increment)	1.06 (1.04 -1.09)	<0.0001	0.99 (0.96-1.02)	0.450
Male Gender	0.79 (0.68 - 0.92)	0.002	0.76 (0.65 - 0.89)	<0.001
Combination MDA	2.45 (1.33 - 4.52)	0.004	2.26 (1.2 - 4.2)	0.010
Namatanai				
Age (by 5-year increment)	1.07 (1.00-1.14)	0.040	1.03 (0.95 - 1.11)	0.470
Male Gender	0.65 (0.44-0.97)	0.001	0.92 (0.56 - 1.49)	0.720
Combination MDA	0.31 (0.02 -4.99)	0.400	0.16 (0.008 - 3.11)	0.227

***Table 3*: Random-effects regression analysis of variables associated with adverse events**
IDA: ivermectin, diethylcarbamazine, and albendazole. **MDA**: mass drug administration.
[a]Coadministration of IDA and azithromycin.

Adverse Events	Combination MDA N=7,281	IDA N=8,375	Azithromycin N=4,228
Any Adverse Event	503 (6.9%)	524 (6.3%)	415 (9.9%)
Fever	15 (0.3%)	32 (0.4%)	43 (1.1%)
Headache	23 (0.4%)	49 (0.6%)	43 (1.1%)
Abdominal Pain	144 (2%)	83 (1%)	191 (4.6%)
Diarrhoea	138 (1.9%)	29 (0.3%)	74 (1.8%)
Nausea	62 (0.9%)	33 (0.4%)	66 (1.6%)
Vomiting	50 (0.7%)	29 (0.4%)	55 (1.4%)
Myalgia	12 (0.2%)	19 (0.3%)	32 (0.8%)
Rash	1 (0.1%)	2 (0.1%)	26 (0.7%)
Itching	2 (0.1%)	6 (0.1%)	1 (0.1%)
Cough	6 (0.1%)	5 (0.1%)	18 (0.5%)
Shortness of Breath	1 (0.1%)	3 (0.1%)	18 (0.5%)
Limb Swelling	1 (0.1%)	2 (0.1%)	17 (0.5%)
Painful Lymphadenopathy	3 (0.1%)	6 (0.1%)	0 (0%)
Fatigue	298 (4.1%)	248 (3.0%)	104 (2.5%)
Dizziness	39 (0.6%)	166 (2.0%)	57 (1.4%)
Allergic Reaction	2 (0.1%)	2 (0.1%)	1 (0.1%)

***Table 4*: Adverse events reported by participants**
IDA: ivermectin, diethylcarbamazine, and albendazole. **MDA**: mass drug administration.
[a]Coadministration of IDA and azithromycin.

combined MDA resulted in higher proportion of AEs (23%) than either of the separate MDAs (11%), overall, the addition of proportions of the two separate MDAs was similar to the combined MDA. It is unclear both programmatically and from a community acceptance perspective whether it would be preferable for communities to experience 20% adverse events at a single time point, or two distinct rounds each of which generate 10% AEs. Reassuringly, AEs in both groups were mild. The most common AEs reported were fatigue and dizziness in the IDA group, gastrointestinal in the AZI group, and all the mentioned three AEs in the combined treatment arm. These AEs are in line with commonly reported side-effects following MDA in other settings. The lack of any serious AEs in a population of more than 15,000 people, and the small number of AEs, indicate that coadministration is a viable means of integrating programmes to control multiple, co-endemic neglected tropical diseases.

Whilst we did not formally set out to compare coverage achieved by a combination MDA to separate MDA, we noted a markedly reduced level of coverage achieved in the AZI MDA conducted one week after IDA MDA, highlighting the difficulty in reaching high levels of compliance in repeated rounds of MDA in remote and rural villages. Reasons for non-compliance to the second round included programme fatigue for longer-running treatment programmes, and other behavioural factors like the need of villagers to prioritize their daily activities for subsistence. Coadministered MDA may overcome these barriers and offer programmes significant logistic advantages.

Our study has a number of limitations. Firstly, enrolment was lower than anticipated, which reduced our power to demonstrate non-inferiority. In particular, a much smaller number of individuals received separate MDA with AZI in Namatanai. Because our study was embedded in programmatic roll-out of MDA we do not have detailed demographic data on individuals who did not attend for the azithromycin MDA or on why they opted to not attend for the second MDA. However, our study is still the largest ever evaluating this approach and provides valuable information to guide NTD programmes. Secondly, due to a low rate of AEs noted in Namatanai District, we altered the approach to asking participants about the side effects of MDA. We found that using a checklist of common side effects yielded up to 10 times more AEs than did an open-ended question. The latter method might have missed mild, transient AEs that had been forgotten by participants at the time they were interviewed 24 hours later. Besides being a limitation of our study, this finding highlights the difficulties in collecting high-quality AE data alongside programmatic MDA. The lower rates of AEs reported in Namatanai are broadly consistent with those obtained in a study evaluating combined MDA with ivermectin and azithromycin in the Solomon Islands[13] but much lower than reported in studies in Mali evaluating combined ivermectin, azithromycin, and albendazole MDA.[14] These findings, together with our observation suggest many individuals do not report mild, self-limiting AEs unless asked specific questions. The importance of such AEs requires further study. We observed individuals only for 24 hours following MDA. This is broadly in keeping with other studies assessing safety of MDA. Whilst we may have missed some late AEs, in the context of a single dose MDA treatment the vast majority of AEs are expected to occur within the first 24 hours, and we therefore do not believe this will have substantially altered our findings. As the study was embedded alongside programmatic MDA blinding was not possible and this should be considered in future studies to reduce the risk of reporting bias. We focused only on safety and not efficacy but as we have previously demonstrated an absence of clinically significant pharmacokinetic interactions, we do not anticipate that the efficacy of combined would be reduced compared to separate MDA.

In summary, our study provides critical data on the programmatic implementation of combined MDA with IDA and AZI compared to separate MDA. Although the AEs rate did not achieve the prespecified non-inferiority margin, the absence of any increase in severe AEs, and higher coverage observed with combined MDA provide some encouragement for implementing this strategy. Further data, either in the context of studies or collected alongside programmatic rollout, will help WHO and

Ministries of Health decide on the optimal use of this approach.

Contributors

LNJ, CGB, MM, OM conceived the study. LNJ, CGB, MVM, RK, WH, JW, MM, OM conducted the study. LNJ, OM, and MM drafted the manuscript. All authors contributed to revising the manuscript.

Declaration of Competing Interest

We declare no competing interests.

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Data sharing statement

An anonymised dataset is available on request to the corresponding author.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.lanwpc.2021.100293.

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