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Individual Efficacy and Community Impact of Ivermectin, Diethylcarbamazine, and Albendazole Mass Drug Administration for Lymphatic Filariasis Control in Fiji: A Cluster Randomized Trial

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Background. Bancroftian filariasis remains endemic in Fiji despite >10 years of mass drug administration (MDA) using diethylcarbamazine and albendazole (DA). The addition of ivermectin to this combination (IDA) has improved efficacy of microfilarial clearance at 12 months in individually randomized trials in nocturnal transmission settings, but impact in a setting of diurnally subperiodic filarial transmission has not been evaluated.

Methods. This cluster randomized study compared the individual efficacy and community impact of IDA vs DA as MDA for lymphatic filariasis in 35 villages on 2 islands of Fiji. Participants were tested at enrollment for circulating filarial antigen and, if positive, for microfilariae. Weight-dosed treatment was offered according to village randomization. Communities were visited at 12 months and retested for lymphatic filariasis. Infected individuals from Rotuma were retested at 24 months.

Results. A total of 3816 participants were enrolled and 3616 were treated. At 12 months, microfilariae clearance was achieved in 72 of 111 participants detected with infection at baseline, with no difference in efficacy between treatment groups: DA, 69.2% (95% confidence interval [CI], 57.2%–79.1%) vs IDA, 62.5% (95% CI, 43.6%–78.2%); risk difference, 11.3 % (95% CI, –10% to 32.7%); $P = .30$. There was no difference between treatment groups in community prevalence of microfilariae at 12 months or individual clearance at 24 months.

Conclusions. We found no difference between IDA and DA in individual clearance or community prevalence of lymphatic filariasis at 12 months, and no improved efficacy following a second annual round of IDA. Possible explanations for the apparent lack of benefit of IDA compared to DA include drug and parasite factors affecting clearance, and higher than expected reinfection rates.

Keywords. lymphatic filariasis; mass drug administration; cluster randomized trial; ivermectin; Fiji.

Wuchereria bancrofti is a parasitic filarial roundworm responsible for the neglected tropical disease lymphatic filariasis (LF). The immature worms, known as microfilariae (Mf), are transmitted between humans by mosquitoes. LF is endemic in 55 countries and is targeted for elimination as a public health problem by the World Health Organization (WHO) [1]. The main strategy to prevent transmission is mass drug administration (MDA) using albendazole, diethylcarbamazine, and ivermectin in a 2-drug combination based on the presence of other endemic pathogens [2].

Diethylcarbamazine and albendazole (DA) has been the standard combination used in Pacific countries. The efficacy of a single round of DA as measured by the clearance of Mf ranges from 7% to 76% at 12 months, 46% to 66% at 24 months, and 83% at 36 months [3–6]. Given the wide range of efficacy at 12 months, multiple annual treatments are recommended to achieve community clearance [7–9]. This approach has been successful in reaching elimination targets in a number of countries, but not in others even after multiple rounds [1].

LF remains endemic in specific areas in Fiji despite many years of control efforts [1]. Complications of the infection were reported from Fiji as early as 1841 [10], and the first national survey in the 1940s observed an Mf prevalence of 12.7% [11]. National MDA with diethylcarbamazine was first introduced in

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1969 [12], after mosquito control strategies had failed to reduce filariasis levels [13, 14]. The national program has adopted DA since 2002.

Coadministration of ivermectin with DA (IDA) has been evaluated in individually randomized trials in Papua New Guinea and Cote d'Ivoire. In Papua New Guinea, 1 round of IDA was superior to DA in clearing Mf with efficacy of at least 96% at 12, 24, and 36 months [3, 15]. In Cote d'Ivoire, efficacy was 71%–87% at 12 months and 61% at 24 months after a single IDA treatment [16, 17]. A large collaborative trial in Fiji, Haiti, India, Indonesia, and Papua New Guinea found that community-wide IDA was as safe as DA [18–20], leading to its adoption for LF elimination programs in certain settings [21]. The superiority of IDA over DA for Mf clearance at 12 months has been reported from the trial sites in Haiti, India, and Papua New Guinea, with IDA efficacy ranging from 84% to 96% compared to DA efficacy of 62% to 83% [20, 22, 23]. However, all of these countries have nocturnal periodic LF transmitted by *Culex* and *Anopheles* vectors, whereas Fiji has transmission that is diurnally subperiodic transmitted by *Culex* and multiple species of *Aedes* mosquitos [24]. Here we report on the 12- and 24-month individual efficacy and the 12-month impact on community LF prevalence of IDA in Fiji.

METHODS

Study Design

We conducted a 3-arm, cluster randomized, open-label safety and efficacy trial involving the whole populations of 2 Fijian islands, Rotuma and Gau (Figure 1) [19]. These islands are within the Eastern Division of Fiji, which has had the highest prevalence of filarial antigenemia [25]. A survey in 2013, after 9 rounds of MDA, found prevalence of 10.5% in Rotuma and 1.6% in Gau (unpublished data, Fiji Centre for Communicable Disease Control).

The study protocol (see the Supplementary Materials) was approved by the Royal Children's Hospital Melbourne Human Research Ethics Committee (reference number 36205) and the Fiji National Health Research and Ethics Review Committee (reference number 2016.81.MC) [19].

Participants

Community engagement with an interactive presentation explaining the study was undertaken in each village. All residents

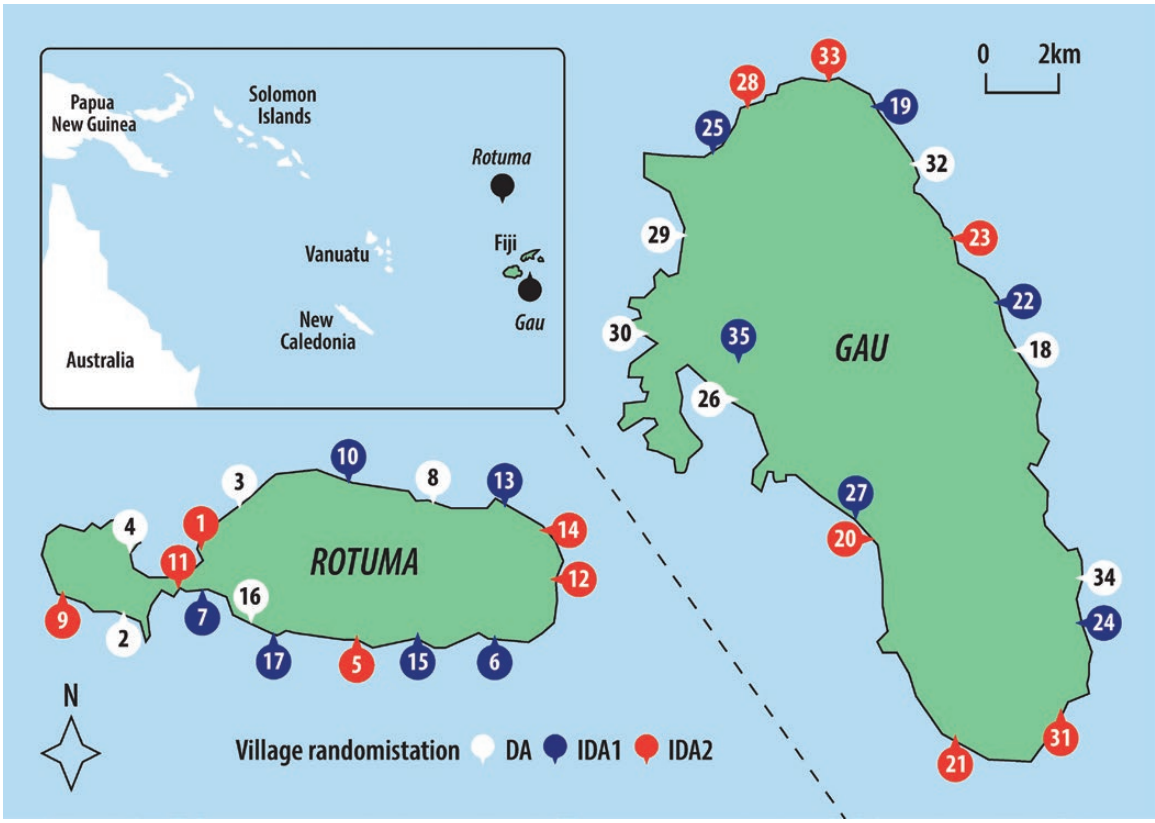

Figure 1. Map of island study sites, village locations, and treatment allocation. Abbreviations: DA, diethylcarbamazine and albendazole; IDA1, ivermectin 1 dose, diethylcarbamazine, and albendazole; IDA2, ivermectin 2 doses, diethylcarbamazine, and albendazole.

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of Rotuma and Gau were invited to their village central meeting place to participate at baseline and 12-month visits.

To measure the prevalence of LF in the entire community 12 months after MDA, people who had not been present at baseline were eligible to be enrolled at 12 months.

To further increase our understanding of Mf clearance in infected individuals from Rotuma, a selective third enrollment took place at 24 months on Rotuma only. Participants with a previous Mf-positive blood smear (at either baseline or 12 months) were eligible.

Written consent was required from all participants and/or guardian. A unique identifier was used to link visits.

Randomization and Blinding

Randomization was at the village level. All 35 villages on both islands agreed to participate (17 on Rotuma and 18 on Gau). Randomization was generated and allocated using Stata software by an independent statistician in a 1:1:1 ratio stratified by island to either DA, IDA1, or IDA2 (IDA at enrollment and a second dose of ivermectin on day 8). The IDA2 group was included to compare the effect of 1 vs 2 doses of ivermectin on community prevalence of scabies. Participants and the study team were unblinded to treatment allocated and received.

Procedures

Prior to receiving medication, participants 2 years and older were tested for filarial infection. The presence of circulating filarial antigen (CFA) was first tested by placing 75 µL of capillary blood onto the rapid test, Alere Filariasis Test Strip (Alere, Scarborough, Maine). CFA positivity was determined by comparing the color strength of the test line against the control at 10 minutes, to give a score of 0 (negative); 1 (weak positive); 2 (medium positive); or 3 (strong positive) [26]. If participants had a negative CFA result, they were assumed to be Mf negative. If participants had a positive CFA result (score 1–3), they had a test for Mf by light microscopy of a 60-µL stained capillary blood smear [9]. Smears were read independently by 2 laboratory technicians, with the average count recorded [9, 27]. Smears with a count discrepancy of >10% were recounted. Mf density estimates per milliliter were calculated by using the Mf count from the smear and multiplying by 16.7 [9].

Exclusion criteria for treatment were age <2 years, weight <15 kg, pregnancy, breastfeeding within 7 days of delivery, severe illness, or allergy to study medications. Participants aged <5 years were also excluded from taking ivermectin in the IDA arm.

Trial drugs were offered at the end of the baseline visit and administered under direct observation in standard doses based on body weight for ivermectin (200 µg/kg) and diethylcarbamazine (6 mg/kg) and as a fixed 400-mg dose for albendazole (Supplementary Table 2).

After assessment at 12 and 24 months, all participants were treated with IDA, the new nationally recommended regimen based on updated WHO guidelines [21], according to the same dosing and exclusion criteria at baseline.

Statistical Analysis

We estimated that the Mf prevalence at baseline would be 1%, equating to at least 13 Mf-positive individuals in each study arm of 1300 enrolled participants. This sample size would provide 80% power to detect superiority of the IDA regimen, based on data from a pilot study that found 90% reduction in Mf prevalence after IDA and 60% reduction after DA [3]. A second dose of ivermectin 1 week after IDA was not expected to change the effect of treatment on adult worms or Mf. We therefore combined IDA1 and IDA2 in the analysis, and compared to DA.

For analyses of efficacy of Mf and CFA clearance at 12 months, only participants who were Mf positive and CFA positive, respectively, at baseline, received treatment, and had filariasis testing at 12 months were included. For 24-month Mf clearance analysis, participants were only from Rotuma and also required treatment at 12 months and testing at 24 months. Participants were grouped according to baseline village randomization. To analyze treatment effect on Mf clearance, we used generalized linear modeling with a log link and binomial distribution, adjusted for clustering by village and stratification by island at 12 months, and for village clustering at 24 months. When assessing other potential contributing factors (island, sex, age, CFA score, and village treatment coverage) on Mf clearance, we did not adjust for stratification by island because models did not converge. We used linear regression adjusted for clustering by village and stratified by island for analysis of the effect of Mf density and medication dose. Comparison of change of CFA semiquantitative scores from baseline to 12 months was done using Pearson χ^2 test.

To assess impact of MDA on community prevalence of LF, the denominator for prevalence calculations was the number of participants tested at each timepoint. Participants were assigned the treatment allocation of the village where they were resident at each timepoint, regardless of treatment they received. Point estimates with 95% confidence intervals (CIs) at each timepoint were adjusted for clustering by village and stratification by island. To calculate absolute reduction in community prevalence, we subtracted 12-month prevalence from baseline prevalence for every village. Risk ratios were calculated using generalized linear models with binomial distribution and log link that adjusted for clustering by village, stratification by island, and baseline prevalence. We used linear regression using cluster-level summaries of prevalence to assess the effect of treatment, treatment coverage,

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baseline prevalence, sex, and island residence on Mf prevalence at 12 months.

Data were analyzed using Stata software version 14.2. The trial was prospectively registered (ClinicalTrials.gov identifier NCT03177993; Australian New Zealand Clinical Trial Registry number N12617000738325).

RESULTS

Baseline visits took place from 13 July to 14 November 2017, 12-month visits from 24 July to 19 November 2018, and 24-month visit to Rotuma only from 19 to 24 October 2019. We had 82% enrollment coverage for baseline and 12 months (Table 1 and Figure 2), with age and sex of participants representative of overall population distribution (Supplementary Tables 3–5. At the 24-month visit, 92 of 131 eligible Mf-positive participants from Rotuma reenrolled (Supplementary Figure 5).

At baseline, CFA screening was performed for 3659 of the eligible 3719 (98.4%) participants aged 2 years and older, and at the 12-month visit, CFA screening was performed for 3773 of the eligible 3786 (99.7%) participants (Supplementary Figure 2). A total of 2816 participants completed CFA screening at baseline and 12 months. Sixty-six participants who were positive for Mf at baseline were tested and treated at all 3 timepoints (Supplementary Table 11 and Supplementary Figure 7).

Baseline filariasis infection characteristics were similar in all 3 treatment groups (14.1% positive for CFA, 3.8% positive for Mf with a geometric mean Mf density of 198/mL (range, 17–9168/mL) (Figures 3 and 4 and Supplementary Tables 6–9) [19]. Mf prevalence was highest in males and adults aged 35–49 years (Supplementary Figures 3 and 8). Rotuma had Mf-positive individuals in 88.2% of villages with village prevalence range of 0–19.3%, compared to Gau with Mf-positive individuals in 61.1% villages and prevalence range of 0–9.2% (Supplementary Table 8 and Supplementary Figure 4). A majority of Mf-positive participants on Gau were from 1 village randomized to DA, with only a few participants with Mf in villages randomized to IDA (Supplementary Tables 7 and 8).

Table 1. Population Coverage for Enrollment and Lymphatic Filariasis Mass Drug Administration at Baseline and 12 Months

		Coverage at Baseline		Coverage at 12 Months	
Study Group	Level of Participation	No.	% of Census	No.	% of Census
DA	Census population	1616	…	1679	…
	Enrolled	1293	80.0	1423	84.8
	Received LF MDA	1216	75.2	1324	78.9
IDA	Census population	2994	…	3073	…
	Enrolled	2519	84.1	2475	80.5
	Received LF MDA	2396	80.0	2344	76.3
All groups	Census population	4610[a]	…	4752[b]	…
	Enrolled	3812	82.7	3898	82.0
	Received LF MDA[c]	3612	78.4	3668	77.2

Abbreviations: DA, diethylcarbamazine and albendazole; IDA, ivermectin, diethylcarbamazine, and albendazole; LF, lymphatic filariasis; MDA, mass drug administration.

[a]Baseline census population: Rotuma, n = 1994; Gau, n = 2616; median village, n = 108 (range, 18–298); median household, n = 5.

[b]Twelve-month census population: Rotuma, n = 2112; Gau, n = 2640; median village, n = 125 (range, 17–310); median household, n = 6.

[c]Treatment coverage by village ranged from 54.4% to 100% at baseline and 56.4% to 88.8% at 12 months (Supplementary Table 4).

Clearance of LF Infection in Individuals

At the 12-month visit, 111 of the 139 (79.9%) Mf-positive participants who received treatment at baseline were retested. Clearance was achieved in 72 individuals (64.9% [95% CI, 51.7%–76.1%]), with Mf clearance by village that ranged from 33.3% to 100%, and there was no significant difference between treatment groups (69.2% vs 62.5% for DA vs IDA, respectively; $P = .30$) (Table 2 and Supplementary Table 6). There was a reduction in mean Mf density in all 3 treatment groups (Supplementary Table 6). The baseline geometric mean density of Mf was >3 times higher in participants who did not achieve Mf clearance compared with those who did (444 vs 128 Mf/mL; $P < .001$). There was no difference in the mean dose per kilogram of weight of medication received between those who did and did not achieve Mf clearance (diethylcarbamazime: 5.9 vs 5.7 mg/kg, respectively, $P = .16$; ivermectin: 195.8 vs 191.5 µg/kg, respectively, $P = .33$). Participants aged 65 years and older were more likely to clear Mf than those aged 35–49 years, as were participants from Gau compared to Rotuma (Table 3). Sex and CFA score were not associated with improved Mf clearance (Table 3). Village treatment coverage was also not associated with Mf clearance ($P = .37$).

There was no difference between treatment groups in changes in CFA score at 12 months ($P = .23$; Figure 4). Of 380 who were positive for CFA at baseline and received treatment, the majority (n = 264 [69.5%]) had a reduction in their CFA score with 153 (40.3%) negative for CFA at 12 months (Table 2).

Of the 92 participants tested at 24 months, 84 (91.3%) were CFA positive, and 53 (58.2%) had cleared Mf based on 3-line blood smear testing (Supplementary Figure 6). In the 66 participants with data at all 3 timepoints, Mf clearance at 24 months was achieved in 12 of 15 (80%) who were treated with DA at baseline and IDA at 12 months, and 27 of 51 (52.9%) who received IDA at both baseline and 12 months ($P = .017$; Supplementary Table 11). In the 27 participants positive for Mf at 24 months, there was a decrease in the geometric mean Mf density over time that was similar between treatment groups (Supplementary Table 13). Of the 24 participants who tested positive for Mf at baseline and 12 months, 6 (25%) were Mf negative at 24 months (Supplementary Table 12). Of the 10 participants positive for Mf at baseline and not treated at 12 months, 2 were negative at 24 months (Supplementary Table 14).

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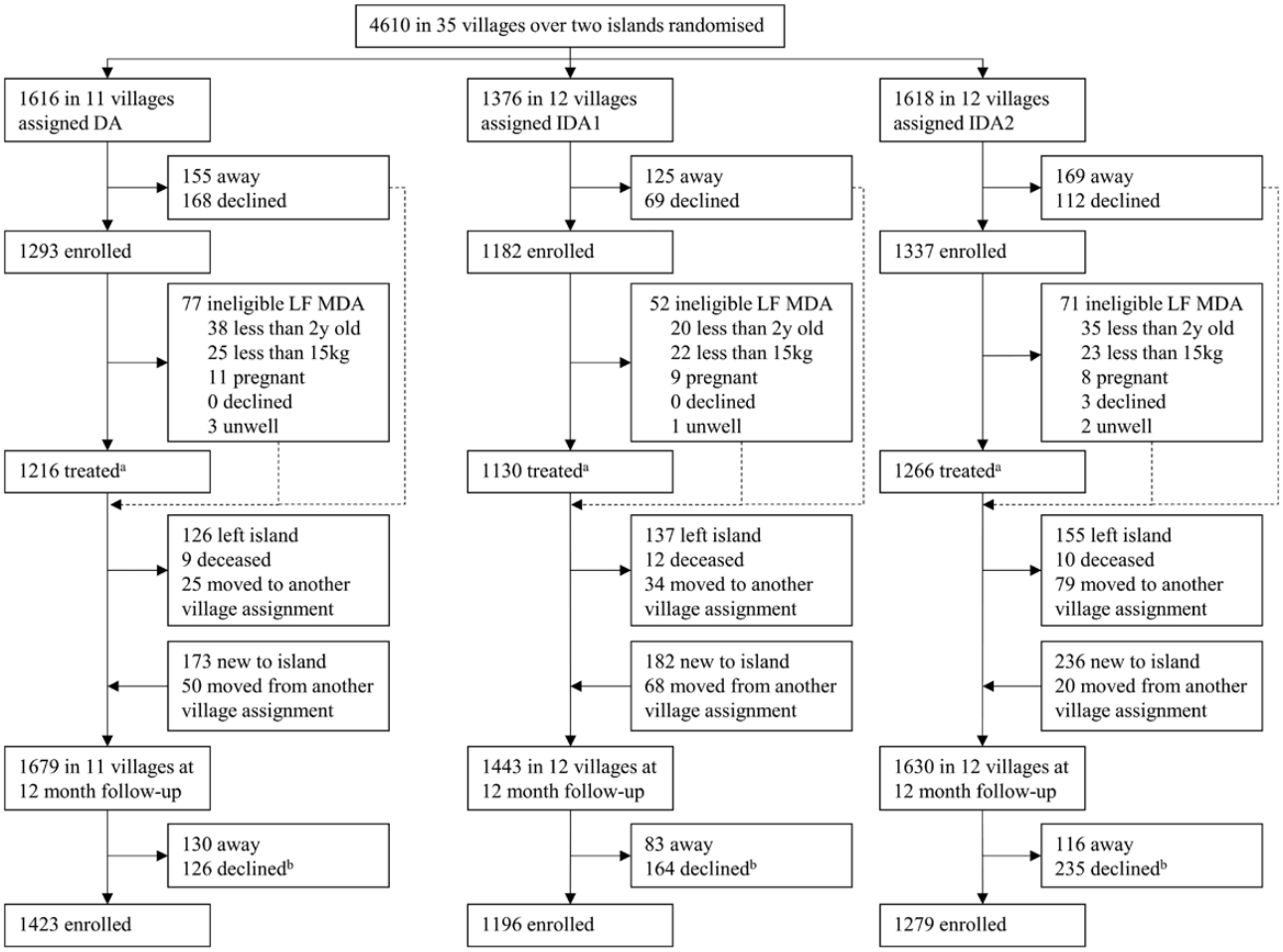

Figure 2. Trial profile detailing village cluster randomization, enrollment and treatment at baseline, and enrollment at 12-month follow-up. [a]Treatment was provided as per village randomization except for 1 person in the diethylcarbamazine and albendazole (DA) group who received ivermectin, diethylcarbamazine, and albendazole (IDA) and 123 in the IDA groups who received DA (due to ineligibility for ivermectin because of weight and/or age). Sixty-one moved between DA and IDA village treatment assignments at 12 months. [b]Of the 525 who declined participation at 12 months, 284 (54%) had previously participated, 159 (30.3%) had previously declined, and 82 (15.6%) were present for the first time and declined. Abbreviations: DA, diethylcarbamazine and albendazole; IDA1, ivermectin 1 dose, diethylcarbamazine, and albendazole; IDA2, ivermectin 2 doses, diethylcarbamazine, and albendazole; LF, lymphatic filariasis; MDA, mass drug administration.

Change in Community Prevalence of Mf

At 12 months, the overall prevalence of Mf in the study population had decreased, with no statistical difference between treatment groups (adjusted absolute reduction: 1.6% [95% CI, .7%–5.2%] for DA vs 1.3% [95% CI, .1%–2.5%] for IDA; $P = .68$) (Table 4 and Supplementary Figure 8). Similarly, there was no statistical difference between treatment groups in the reduction of community CFA prevalence at 12 months (adjusted absolute reduction: 6.9% [95% CI, 4.4%–9.3%] for DA vs 4.6% [95% CI, 2.6%–6.5%] for IDA; $P = .10$) (Table 4 and Supplementary Figure 8).

High baseline community Mf prevalence was associated with a higher community Mf prevalence at 12 months ($P < .001$). There was no effect observed for village treatment allocation ($P = .63$), treatment coverage ($P = .52$), or sex ($P = .25$).

DISCUSSION

In the first reported comparison of IDA vs DA in a setting of diurnally subperiodic LF, we found no difference in individual clearance of Mf at 12 months between groups. Similarly, there was no added benefit of IDA on community Mf prevalence at 12 months. The efficacy of both treatments for Mf clearance at 12 months was comparable to the highest reported efficacy for DA [6]. Among participants from Rotuma who were positive for Mf 12 months after the first round of treatment, we did not observe an increased level of clearance 12 months after a second round of IDA.

Our findings contrast with previous reports of superior efficacy of IDA compared to DA. There are several possible explanations for the apparent lesser effect of IDA in our study, broadly divided into factors that may contribute to reduced clearance in individuals, or reinfection.

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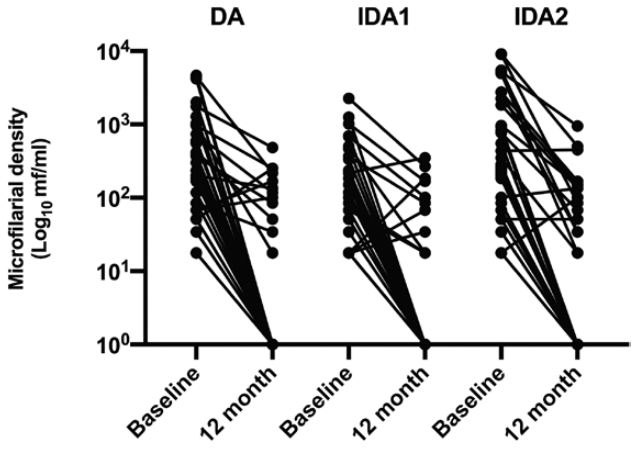

Figure 3. Individual efficacy of different treatments on lymphatic filariasis comparing baseline to 12 months and grouped by baseline village randomization. Microfilarial density: a log of the estimate microfilariae (Mf) density in 1 mL of blood. Increased Mf density at 12 months, n = 10 (9%); diethylcarbamazine and albendazole, n = 3 (7.7%); ivermectin, diethylcarbamazine, and albendazole, n = 7 (9.7%). Geometric mean Mf density changed from 53 (range, 17–434) Mf/mL to 143 (range, 33–451) Mf/mL. Abbreviations: DA, diethylcarbamazine and albendazole (n = 39); IDA1, ivermectin 1 dose, diethylcarbamazine, and albendazole (n = 35); IDA2, ivermectin 2 doses, diethylcarbamazine, and albendazole (n = 37).

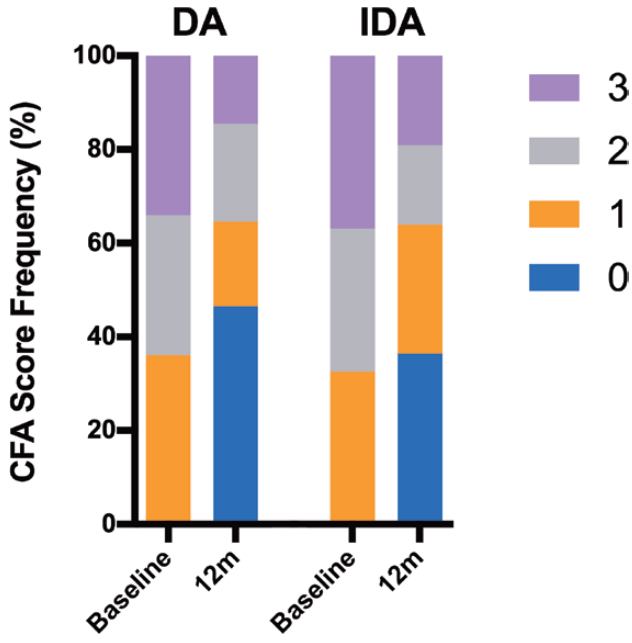

Figure 4. Change in semi-quantitative circulating filarial antigen score over time by treatment group. Circulating filarial antigen (CFA) semi-quantification score: 0, negative; 1, weak positive; 2, medium positive; 3, strong positive. Frequency is a percentage of total of those CFA positive at baseline, treated, and a score recorded at 12 months (n = 380); increased score n = 7 (1.8%, 0.7% for diethylcarbamazine and albendazole [DA] vs 2.5% for ivermectin, diethylcarbamazine, and albendazole [IDA]); no change in score: n = 109 (28.7%, 25.7% for DA vs 30.5% for IDA). Abbreviations: CFA, circulating filarial antigen; DA, diethylcarbamazine and albendazole; IDA, ivermectin, diethylcarbamazine, and albendazole.

Clearance of infection is related to choice of medication, host, and parasite factors. All medications were sourced from reputable sources and stored at recommended temperatures, and administered under direct observation at adequate doses by weight. Our study population had a higher mean body mass index compared to other countries in the IDA community trials [28]; however, body fat percentage has not been shown to affect ivermectin pharmacokinetics [29]. Diet may have altered the absorption and/or metabolism of the medications, but we would expect this to be a random effect balanced across treatment groups [30]. The population of Rotuma, a very remote island in the Pacific, may have host genetic factors that contribute to altered metabolism, and hence reduced efficacy of the medications [31]. Ivermectin is not widely available in Fiji, so parasite resistance to ivermectin as a result of human consumption is unlikely. It is possible for subpopulations of adult *W. bancrofti* that form worm nests within infected individuals to be resistant to treatment, as observed in Brazil and Cote d'Ivoire [17, 32]. This could explain our observation of reduced geometric mean Mf density without clearance, and the reduced Mf clearance after a second round of IDA in individuals who failed to clear after the first round of treatment.

Reinfection is possible in this high-prevalence setting, supported by evidence of ongoing transmission with new infections appearing in children. There are several potential factors to explain why participants in our study may have had a higher likelihood of reinfection compared to populations included in other IDA efficacy studies. First, individuals in Fiji are at risk of exposure to parasite-carrying mosquitos throughout both day and night because filariasis is diurnally subperiodic [33]. Second, the predominant *Aedes* mosquito in Fiji has the ability to efficiently transmit the parasite following a blood meal when Mf density is low in the human host [24, 34]. Third, there are no vector control interventions (eg, long-lasting insecticide-treated bed nets) implemented as public health strategies for LF control in Fiji, in contrast to Papua New Guinea and Cote d'Ivoire, which have nocturnal LF transmission and active bed net programs for malaria control. In other countries with diurnally subperiodic LF, the strategy of MDA without addressing vector control has been cautioned [35].

There are several strengths of our study. First, we are confident that oral study medications were administered because they were provided as directly observed therapy. Second, loss to follow-up was very low, specifically among Mf-positive participants. Third, the same laboratory technician read all smears at all timepoints, eliminating interreader variability of Mf counts. There are also limitations to our study. First, it was not possible to blind our participants or assessors to treatment randomization. Second, the baseline prevalence of LF differed between treatment groups on Gau, an island with overall low prevalence. There had been no recent comprehensive island LF surveys conducted, so we were not able to accurately predict and account

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Table 2. Efficacy of Different Treatments on Clearance of Circulating Filarial Antigen and Microfilariae at 12 Months

		No. of Participants		Rate of Clearance		Risk Difference[b]		
Measure of Infection	Treatment	Positive Baseline	Negative at 12 mo[a]	%	(95% CI)[b]	%	(95% CI)	*P* Value
Mf clearance[c]	DA	39	27	69.2	(57.2–79.1)	Control	…	
	IDA	72	45	62.5	(43.6–78.2)	11.3	(–10.0 to 32.7)	.30
CFA clearance[d]	DA	144	67	46.5	(30.7–63.1)	Control	…	
	IDA	236	86	36.4	(29.8–43.7)	–3.1	(–19.5 to 13.3)	.71

Abbreviations: CFA, circulating filarial antigen; CI, confidence interval; DA, diethylcarbamazine and albendazole; IDA, ivermectin, diethylcarbamazine, and albendazole; Mf, microfilarial.

[a]Participants grouped according to baseline randomization and treatment and not village residency at 12-month visit.

[b]Adjusted for clustering by village and stratification by island.

[c]Excludes n = 1 in DA group (not treated).

[d]Excludes n = 2 in DA group and n = 1 in IDA group (not treated).

for high prevalence localities in the randomization. Many of the Mf-positive participants on Gau lived in a single village randomized to DA, and this limited the reliability of any inter-island treatment effect comparisons. Third, treatment randomization of clusters rather than individuals or households may not have eliminated the possibility of residual confounding.

Scrotal ultrasounds have been used to detect and monitor the impact of medications on worm nests [16, 17]. This technique may have helped to distinguish between failure to clear infections present at baseline and reinfection over the course of the study. Similarly, molecular xenomonitoring of mosquitos for filarial DNA may have provided additional information on transmission dynamics in our villages. Utilization of these tools could enhance our understanding of the impact on individuals and communities in future implementation of MDA and transmission assessments.

Despite the finding in our study that the reduction in community burden of LF at 12 months was comparable between treatment groups, successive rounds of MDA remain a valuable strategy to achieve a reduction in community prevalence of LF. The addition of ivermectin to DA, while not adding benefit for filariasis control in our study, has the potential to impact other neglected tropical diseases, notably scabies and soil-transmitted helminths [2, 36–39]. Seeking treatment for these symptomatic infections may motivate participation in successive rounds of MDA and lead to increased success for LF control.

Our findings emphasize the importance of multicenter, community-based studies in varied settings, including those with diurnally subperiodic transmission by predominantly aedine vectors. Repeating IDA efficacy studies in other areas with diurnally subperiodic LF will be important to better understand the reasons for our findings. Our study will influence policy decision-making in Fiji, and potentially in other settings with similar transmission dynamics, regarding the number of MDA rounds needed to achieve elimination and community

Table 3. Factors Associated With Clearance of Microfilariae

				Univariate Analysis[a]	
Factor	Mf Positive at Baseline, No.	Mf Negative at 12 mo, No.	%	Risk Difference, %	(95% CI)
Island					
Rotuma	84	49	58.3	Ref	…
Gau	27	23	85.2	35.1	(16.6–53.5)
Sex					
Male	90	55	61.1	Ref	…
Female	21	17	81.0	19.0	(–.6 to 38.6)
Age					
5–24	8	5	62.5	1.3	(–24.2 to 26.9)
25–34	15	11	73.3	10.5	(–9.8 to 30.9)
35–49	42	26	61.9	Ref	
50–64	30	16	53.3	–8.6	(–31.7 to 14.4)
≥65	16	14	87.5	24.7	(2.1–47.3)
Lymphatic filariasis					
CFA1 (weak positive)	6	5	83.3	Ref	…
CFA2 (medium positive)	23	19	82.6	–3.6	(–41.7 to 34.5)
CFA3 (strong positive)	82	48	58.5	–27.8	(–64.0 to 8.4)

Abbreviations: CFA, circulating filarial antigen; CI, confidence interval; Mf, microfilariae.

[a]Generalized linear modeling adjusting for clustering by village (denominator: n = 111).

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Table 4. Effectiveness of Different Treatments on Community Prevalence of Lymphatic Filariasis at 12 Months

		Prevalence at Baseline[a]				Prevalence at 12 mo[a]				Absolute Reduction[b]		Risk Ratio[c]	
Measure of Infection	Treatment	No.	No.	%	(95% CI)	No.	No.	%	(95% CI)	%	(95% CI)	%	(95% CI)
Mf positive[d]	DA	1238	47	3.8	(1.5–9.1)	1372	26	1.9	(.7–5.2)	1.6	(.3–2.9)	1	(Ref)
	IDA	2399	93	3.9	(2.6–5.8)	2398	46	1.9	(1.0–3.6)	1.3	(.1–2.5)	0.8	(.5–1.3)
CFA positive[e]	DA	1239	186	15.0	(8.8–24.4)	1372	109	7.9	(3.5–17.1)	6.9	(4.4–9.3)	1	(Ref)
	IDA	2420	330	13.6	(10.0–18.3)	2401	211	8.8	(6.2–12.3)	4.6	(2.6–6.5)	1.1	(.8–1.4)

Abbreviations: CFA, circulating filarial antigen; CI, confidence interval; DA, diethylcarbamazine and albendazole; IDA, ivermectin, diethylcarbamazine, and albendazole; Mf, microfilariae.

[a]Adjusted for clustering on village and stratified by island. Mf positive at 12 months: n = 72 (n = 40 Mf positive at baseline; n = 11 Mf negative or Mf unknown at baseline; n = 21 absent at baseline); CFA positive at 12 months for the first time: n = 91 (n = 17 previously CFA negative; n = 1 not eligible for testing at baseline; n = 73 absent at baseline).

[b]Adjusted for clustering on village.

[c]Adjusted for clustering by village, stratified by island and baseline Mf prevalence.

[d]Mf denominator: baseline, n = 3637 (excludes n = 71 declined, n = 93 ineligible, n = 11 unreadable); 12 months, n = 3770 (excludes n = 15 declined, n = 112 ineligible, n = 1 unreadable). Participants are grouped into the village randomization where they were resident at time of testing; n = 225 Mf smears both timepoints; n = 286 at baseline only; n = 93 at 12 months only.

[e]CFA denominator: baseline, n = 3659 (excludes n = 60 declined, n = 93 ineligible); 12 months, n = 3773 (excludes n = 13 declined, n = 112 ineligible). Participants are grouped into the village randomization where they were resident at time of testing; n = 2816 tested at both timepoints; n = 843 tested at baseline only; n = 957 tested at 12 months only.

messaging alongside these new policies. Ultimately, further research into different strategies in different settings remains crucial to achieving elimination of filariasis around the world.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. M. H., J. S., A. C. S., G. J. W., C. L. K., J. M. K., and L. J. R. contributed to the design of the study. M. H. was the primary coordinator of data collection and analysis and the primary author of the manuscript. A. C. S., J. M. K., and L. J. R. supervised data collection, analysis, interpretation, and manuscript writing. Fieldwork was supported by J. S., M. K., M. T., L. R., and M. J. W. Data analysis was supported by A. C. G. All authors contributed to the writing of the manuscript and approved the final version.

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