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Mass Drug Administration for Scabies Control in a Population with Endemic Disease

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ABSTRACT

BACKGROUND

Scabies is an underrecognized cause of illness in many developing countries. It is associated with impetigo, which can lead to serious systemic complications. We conducted a trial of mass drug administration for scabies control in Fiji.

METHODS

We randomly assigned three island communities to one of three different interventions for scabies control: standard care involving the administration of permethrin to affected persons and their contacts (standard-care group), mass administration of permethrin (permethrin group), or mass administration of ivermectin (ivermectin group). The primary outcome was the change in the prevalence of scabies and of impetigo from baseline to 12 months.

RESULTS

A total of 2051 participants were enrolled; 803 were in the standard-care group, 532 in the permethrin group, and 716 in the ivermectin group. From baseline to 12 months, the prevalence of scabies declined significantly in all groups, with the greatest reduction seen in the ivermectin group. The prevalence declined from 36.6% to 18.8% in the standard-care group (relative reduction in prevalence, 49%; 95% confidence interval [CI], 37 to 60), from 41.7% to 15.8% in the permethrin group (relative reduction, 62%; 95% CI, 49 to 75), and from 32.1% to 1.9% in the ivermectin group (relative reduction, 94%; 95% CI, 83 to 100). The prevalence of impetigo also declined in all groups, with the greatest reduction seen in the ivermectin group. The prevalence declined from 21.4% to 14.6% in the standard-care group (relative reduction, 32%; 95% CI, 14 to 50), from 24.6% to 11.4% in the permethrin group (relative reduction, 54%; 95% CI, 35 to 73), and from 24.6% to 8.0% in the ivermectin group (relative reduction, 67%; 95% CI, 52 to 83). Adverse events were mild and were reported more frequently in the ivermectin group than in the permethrin group (15.6% vs. 6.8%).

CONCLUSIONS

Mass drug administration, particularly the administration of ivermectin, was efficacious for the control of scabies and impetigo. (Funded by the Australian National Health and Medical Research Council; Australian New Zealand Clinical Trials Registry number, ACTRN12613000474752.)

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Scabies, a skin condition that is recognized by the World Health Organization as a disease of public health importance,[1] is a substantial contributor to global morbidity and mortality. Scabies is caused by a microscopic mite (*Sarcoptes scabiei* var. *hominis*) and is transmitted primarily through person-to-person contact. Infestation can result in debilitating itchiness, with associated sleep disturbance, reduced ability to concentrate,[2] social stigmatization,[3] and ongoing health care expenses.[4,5]

In many developing countries, scabies-related scratching is an important cause of impetigo,[6-10] which is most often due to *Streptococcus pyogenes* or *Staphylococcus aureus* infection and can lead to septicemia, glomerulonephritis, and rheumatic heart disease.[11] An estimated 100 million persons have scabies worldwide; most live in tropical countries,[12] and those living in the Pacific Islands are particularly affected.[10,13-16]

Effective treatments, both topical and oral, are available for scabies. However, among persons who live in regions where the pathogen is endemic, reinfestation can occur rapidly, even when household contacts are also treated.[17] Mass drug administration, which generally involves repeat administration of single-dose therapeutic agents to whole communities, has become a central strategy for the control of several neglected tropical diseases.[1,18] Single-group studies of the mass administration of topical permethrin[6,8] and ivermectin (an oral agent that is the drug of choice for mass administration for onchocerciasis and lymphatic filariasis)[7,19-24] have shown promise. To strengthen the evidence base for mass drug administration for scabies control, we undertook a comparative trial called the Skin Health Intervention Fiji Trial (SHIFT).

METHODS

STUDY POPULATION

We conducted SHIFT in Fiji from September 2012 through September 2013. After consultation with health authorities, we identified three island communities as study groups (Fig. 1), on the basis of relative isolation, population size (small enough to be manageable but large enough to provide study power), and cultural similarities.[25] One community occupies a single island, the second occupies two neighboring islands, and the third occupies three islands. Each community has one nurse-staffed clinic.

STUDY PROCEDURES

The three island communities were randomly assigned, through the drawing of lots, to one of three different interventions for scabies control: standard care involving the administration of permethrin to affected persons and their contacts (standard-care group), mass administration of permethrin (permethrin group), or mass administration of ivermectin (ivermectin group). The study procedures were the same across communities and involved visits at baseline and at 12 months for all residents and a visit at 3 months for a random sample of 20% of each group. Each visit took place during a scheduled week.

All residents were eligible to participate. The residents were identified with the use of a 2012 population list provided by the study nurse; they were invited by letter to participate and then visited by the local district nurse if they were present in the community. When the study team arrived for the baseline visit, all residents who were present at the time were invited to enroll in the study. Those who provided consent to participate gave basic sociodemographic information and a brief medical history. When the study team returned for the 12-month visit, all residents who were present in the community were again approached by the study team. The residents who had enrolled in the study at baseline were reexamined and asked about any absences from the community since enrollment. The residents who were present but had not enrolled in the study at baseline were invited to enroll. At the baseline, 3-month, and 12-month visits, a skin examination of consenting participants was performed by the study nurse.

For the groups that underwent mass drug administration, data on adverse events were obtained through direct questioning of participants 7 to 14 days after the drug was administered. During the periods before and after the drug was administered, we used routinely collected health service data to record the number of patients who presented to community clinics with any skin condition and the number of clinic referrals to major health centers.

In accordance with the Integrated Management of Childhood Illness (IMCI) guidelines,[13] scabies was defined as the presence of pruritic inflammatory papules with a typical anatomical distribution (e.g., on the webs of the fingers, hands, wrists, or ankles).[26] Examination of the breasts and genitals was performed only when

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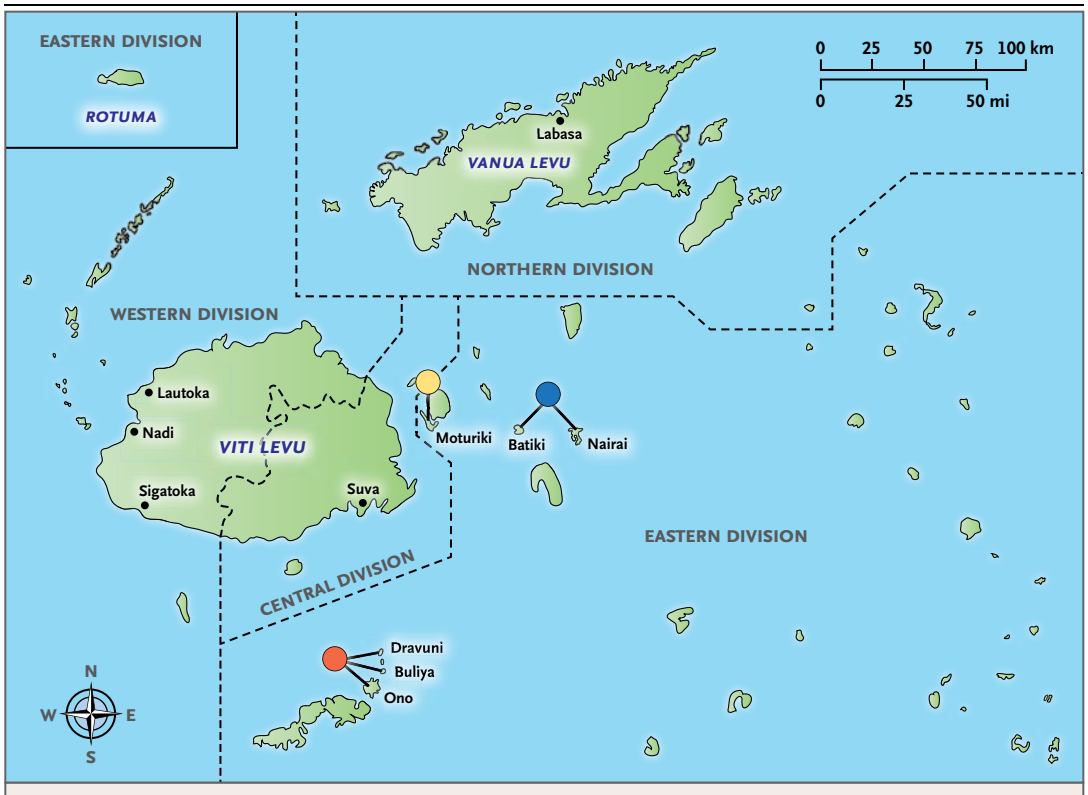

Figure 1. Study Sites in Fiji.

The figure shows the locations of the three island communities that were included in the study. The yellow pin indicates the site of the standard-care group, the red pin the sites of the permethrin group, and the blue pin the sites of the ivermectin group.

requested by participants and in a separate, private space. Determination of the severity of scabies was based on the number of lesions, in categories of mild (≤10), moderate (11 to 49), and severe (≥50). Infected scabies was defined as scabies plus the presence of pus-filled or crusted papules. If crusted ("Norwegian") scabies was suspected, a scraping of the skin was obtained for microscopic examination for mites, and a photograph was sent to the team's clinical advisors (the second and last authors). Impetigo was defined as the presence of a papular, pustular, or ulcerative lesion surrounded by erythema.

INTERVENTIONS

Standard-Care Group

Participants in the standard-care group who had scabies at baseline were referred to the local clinic for guideline-recommended treatment with one dose of topical permethrin cream, with a second dose provided after 14 days if symptoms persisted. The guidelines also recommended a single dose of permethrin for the patient's contacts.[13] We provided permethrin cream to the local clinics to ensure that the supply would be adequate.

Permethrin Group

All participants in the permethrin group were offered one dose of topical permethrin cream followed by a second dose 7 to 14 days later if scabies had been observed at baseline. For younger children, parents were asked to apply the cream under the direct observation of study staff. Older children and adults were encouraged to apply the cream in the clinic but could apply it at home. Participants were asked to apply the cream from neck to toes and to leave it on for 8 to 24 hours (or for 4 hours in the case of participants <2 months of age). In infants, the cream was also applied to the scalp.

Ivermectin Group

All participants in the ivermectin group were offered one dose of oral ivermectin (200 μg per kilogram of body weight), which was taken under

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the direct observation of study staff. Ivermectin was replaced with topical permethrin cream in the following participants: children who weighed less than 15 kg, women who were pregnant or breast-feeding,[27] persons with neurologic disease, and persons taking medications that are metabolized by the cytochrome P-450 pathway, including warfarin and some anticonvulsant agents. For participants who had scabies at baseline, a second dose of the medication that had been provided at baseline was distributed by study staff 7 to 14 days after the initial dose was administered.

Treatment for crusted scabies consisted of the administration of two doses of ivermectin 1 week apart and the administration of permethrin cream twice a week for 1 month, with follow-up at 1, 2, 3, and 12 months.[28] All participants with crusted or purulent impetigo lesions were referred to clinics in order to receive antibiotic agents, in accordance with Fiji IMCI guidelines.[13] Participants in all groups could present to their community clinic at any time and receive standard care with permethrin.

STUDY OUTCOMES

The primary outcome was the change in the prevalence of scabies and of impetigo from baseline to 12 months. Prevalence was calculated at baseline and 12 months with the use of data from the entire sample of participants at each time point.

Safety outcomes were based on adverse events, which were classified as serious if they were immediately life threatening, led to hospitalization, or resulted in persistent or substantial disability or death. We established an independent safety committee that consisted of academic physicians, including a Fijian representative. Adverse events were reviewed by the local study doctor, with subsequent referral to the safety committee.

STUDY OVERSIGHT

The trial was approved by the Fijian National Research Ethics Committee and the Royal Children's Hospital Human Research Ethics Committee. There was a delay in meeting registration deadlines for the study because the investigators initially were of the understanding that community-intervention studies of this kind, as opposed to individually randomized trials, do not require registration. Written informed consent was obtained from all participants. Merck Sharp and Dohme (Australia) provided the ivermectin but had no other role in the study. The Fiji Ministry of Health and Medical Services provided paid personnel. The study was designed by the authors. All the authors vouch for the integrity and completeness of the data and analyses and for the fidelity of the study to the protocol (available with the full text of this article at NEJM.org).

STATISTICAL ANALYSIS

We calculated the change in prevalence of scabies and of impetigo in each of the three study groups. We calculated both the absolute reduction (the difference between the prevalence at 12 months and the prevalence at baseline) and the relative reduction (the ratio of the prevalence at 12 months to the prevalence at baseline). Confidence intervals for the reductions were calculated with the use of the variance of the binomial distribution.[29] To compare the study groups, we calculated the ratio of the prevalence at 12 months to the prevalence at baseline in each group and then tested the null hypothesis that these ratios were equal.[30] All tests were two-sided. Among participants who were examined at both baseline and 12 months, we calculated the rates of the appearance of scabies (the proportion of persons without scabies at baseline who had scabies at 12 months) and the disappearance of scabies (the proportion of persons with scabies at baseline who did not have scabies at 12 months). Safety outcomes were summarized as proportions of participants in each group who had adverse events.

Study power and sample size were based on estimates from previous research conducted in Fiji. We estimated that the prevalence of scabies would be 23% at baseline and that the prevalence would fall to 5% in the groups that underwent mass drug administration[6-8] and to 10% in the standard-care group.[16,31] Assuming an 80% response rate in each group and a 20% loss to follow-up at 12 months, we estimated that a sample of 1920 participants would give the study more than 90% power to detect the estimated differences at a two-sided significance level of 0.05.

RESULTS

STUDY POPULATION

A total of 2051 persons consented to participate in the study (Table 1), representing more than 85% of the resident population of the three com-

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Table 1. Characteristics of the Participants at Baseline and 12 Months.*

Characteristic	Ivermectin Group		Permethrin Group		Standard-Care Group		All Groups	
	Baseline (N=716)	12 Mo (N=587)	Baseline (N=532)	12 Mo (N=449)	Baseline (N=803)	12 Mo (N=746)	Baseline (N=2051)	12 Mo (N=1782)
Median age (IQR) — yr	24 (8–44)	24 (8–44)	25 (8–47)	26 (8–50)	22 (8–44)	25 (8–45)	24 (8–45)	25 (8–46)
Age — no. (%)								
<5 yr	86 (12.0)	71 (12.1)	70 (13.2)	56 (12.5)	101 (12.6)	97 (13.0)	257 (12.5)	224 (12.6)
5–9 yr	134 (18.7)	123 (21.0)	83 (15.6)	80 (17.8)	124 (15.4)	118 (15.8)	341 (16.6)	321 (18.0)
10–14 yr	96 (13.4)	73 (12.4)	60 (11.3)	50 (11.1)	121 (15.1)	88 (11.8)	277 (13.5)	211 (11.8)
15–24 yr	44 (6.1)	25 (4.3)	49 (9.2)	29 (6.5)	75 (9.3)	65 (8.7)	168 (8.2)	119 (6.7)
25–34 yr	106 (14.8)	81 (13.8)	69 (13.0)	56 (12.5)	105 (13.1)	100 (13.4)	280 (13.7)	237 (13.3)
≥35 yr	250 (34.9)	214 (36.4)	201 (37.8)	178 (39.6)	277 (34.5)	278 (37.3)	728 (35.5)	670 (37.6)
Sex — no. (%)								
Male	385 (53.8)	309 (52.6)	274 (51.5)	235 (52.3)	405 (50.4)	381 (51.1)	1064 (51.9)	925 (51.9)
Female	331 (46.2)	278 (47.4)	258 (48.5)	214 (47.7)	398 (49.6)	365 (48.9)	987 (48.1)	857 (48.1)
Persons in household — median (IQR)	5 (4–7)	NA	5 (4–6)	NA	5 (4–7)	NA	5 (4–7)	NA
≥1 Off-island trip in the previous 12 mo — no. of persons (%)	NA	158 (26.9)	NA	267 (59.5)	NA	232 (31.1)	NA	657 (36.9)

* IQR denotes interquartile range, and NA not applicable.

munities (for details about residents who did not participate in the study, see Table S1 in the Supplementary Appendix, available at NEJM.org). The distributions of age and sex were similar across the communities (Table 1); 99.7% of the residents in these communities were indigenous Fijians (iTaukei). Loss to follow-up at 12 months was higher in the standard-care group than in the permethrin and ivermectin groups (28.3% vs. 25.0% and 21.6%, respectively) (Fig. 2, and Table S2 in the Supplementary Appendix). At 12 months, an additional 246 participants were enrolled, with enrollment higher in the standard-care group than in the permethrin and ivermectin groups (170 persons vs. 50 and 26, respectively).

In the ivermectin group, 623 of the 716 participants received ivermectin under the direct observation of study staff, and 93 received permethrin, in accordance with the exceptions specified in the protocol. Of these 93 participants, 55 were younger than 5 years of age, 27 were lactating, 8 were pregnant, and 3 had other contraindications; the application of permethrin was directly observed in 61 of these participants, and thus therapy was administered to 96% of the ivermectin group under direct observation. The 230 participants in this group who had scabies at baseline received a second treatment; 200 received ivermectin and 30 received permethrin, and all the interventions were administered under direct observation.

In the permethrin group, 307 of the 532 participants (58%) received treatment under direct observation, and 181 of the 222 participants who had scabies at baseline (82%) received a second treatment. No data on the use of permethrin were collected for the standard-care group, since all treatment was administered in the community clinic.

PREVALENCE OF SCABIES AND IMPETIGO

At baseline, the prevalence of scabies was highest in the permethrin group, at 41.7% (Table 2). Among participants with scabies, the severity at baseline was similar across groups; 62% had fewer than 10 lesions, and 10% had 50 lesions or more. Scabies most commonly involved the hands (in 64%), arms (in 38%), feet (in 29%), and legs (in 26%). There was one diagnosis of crusted scabies in the entire study population, in the standard-care group.

At 12 months, the prevalence of scabies had declined in all study groups, with the greatest decline observed in the ivermectin group. The relative reduction in the prevalence of scabies was 94% (95% confidence interval [CI], 83 to

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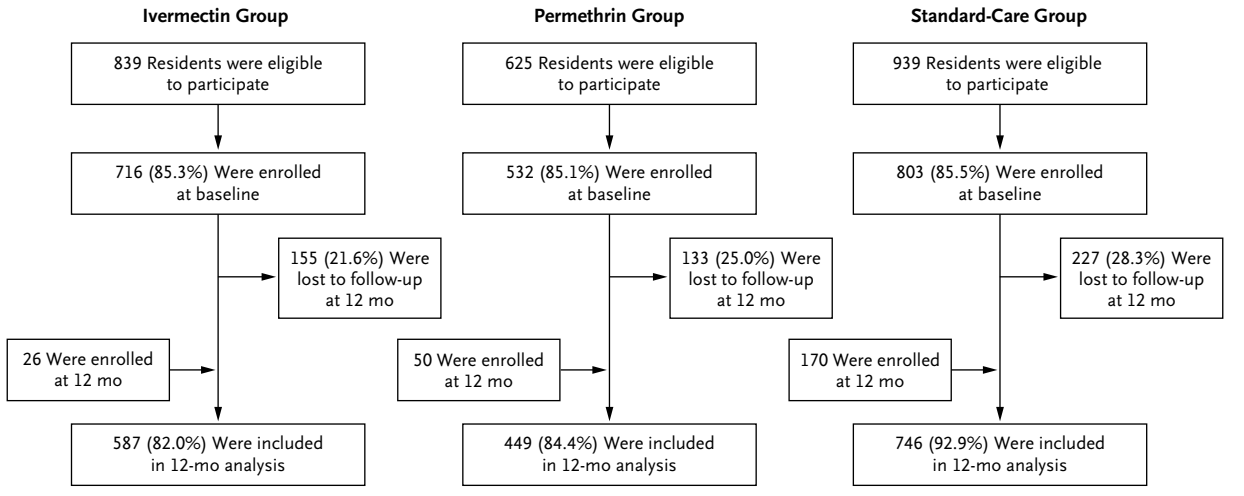

Figure 2. Enrollment and Follow-up.
The persons enrolled at 12 months were residents who were present at the 12-month visit but had not been present at baseline.

Table 2. Prevalence of Scabies and Impetigo at Baseline and 12 Months.*

Study Group	Prevalence at Baseline		Prevalence at 12 Mo		Absolute Reduction in Prevalence	Relative Reduction in Prevalence
	no./total no.	*% (95% CI)*	*no./total no.*	*% (95% CI)*	*percentage points (95% CI)*	*% (95% CI)*
Ivermectin						
Scabies	230/716	32.1 (28.8–35.6)	11/587	1.9 (0.9–3.3)	30.2 (26.6–33.9)	94 (83–100)
Impetigo	176/716	24.6 (21.6–27.9)	47/587	8.0 (6.1–10.5)	16.6 (12.7–20.4)	67 (52–83)
Permethrin						
Scabies	222/532	41.7 (37.6–46.0)	71/449	15.8 (12.6–19.5)	25.9 (20.4–31.2)	62 (49–75)
Impetigo	131/532	24.6 (21.2–28.5)	51/449	11.4 (8.8–14.6)	13.3 (8.5–17.9)	54 (35–73)
Standard care						
Scabies	294/803	36.6 (33.4–40.0)	140/746	18.8 (16.0–21.8)	17.8 (13.4–21.5)	49 (37–60)
Impetigo	172/803	21.4 (18.7–24.4)	109/746	14.6 (12.3–17.3)	6.8 (3.0–10.6)	32 (14–50)

* The absolute reduction is the difference between the prevalence at 12 months and the prevalence at baseline, and the relative reduction is the ratio of the prevalence at 12 months to the prevalence at baseline. CI denotes confidence interval.

100) in the ivermectin group, as compared with 62% (95% CI, 49 to 75) in the permethrin group ($P<0.001$) and 49% (95% CI, 37 to 60) in the standard-care group ($P<0.001$); the difference between the permethrin group and the standard-care group was not significant ($P=0.09$). The combined relative reduction in the two groups that underwent mass drug administration was 78% (95% CI, 69 to 87).

The reduction in the prevalence of scabies was similar when participants who were enrolled at 12 months were included in or excluded from the analysis (Table S3 in the Supplementary Appendix). In all groups, there was a reduction in the prevalence across all age groups and both sexes (Tables S4 and S5 in the Supplementary Appendix), as well as a reduction in the proportion of scabies cases that were categorized as severe (≥50 lesions) (Table S6 in the Supplementary Appendix).

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Table 3. Rates of Disappearance and Appearance of Scabies among Participants Who Were Examined at Both Baseline and 12 Months.

Study Group	Disappearance of Scabies			Appearance of Scabies		
	Scabies Present at Baseline	Scabies Absent at 12 Mo	Rate of Disappearance	Scabies Absent at Baseline	Scabies Present at 12 Mo	Rate of Appearance
	no. of patients		*% (95% CI)*	*no. of patients*		*% (95% CI)*
Ivermectin	187	182	97.3 (93.9–99.1)	374	5	1.3 (0.4–3.1)
Permethrin	174	130	74.7 (67.6–81.0)	225	18	8.0 (4.8–12.3)
Standard care	218	161	73.9 (67.5–79.6)	358	55	15.4 (11.8–19.5)

At baseline, the prevalence of impetigo was 21.4% in the standard-care group and 24.6% in the combined groups that underwent mass drug administration (Table 2). At 12 months, the prevalence of impetigo had declined in all study groups, with the greatest decline observed in the ivermectin group. The relative reduction in the prevalence of impetigo was 67% (95% CI, 52 to 83) in the ivermectin group, as compared with 54% (95% CI, 35 to 73) in the permethrin group ($P=0.26$ for the comparison with the ivermectin group) and 32% (95% CI, 14 to 50) in the standard-care group ($P=0.05$ for the comparison with the ivermectin group); the difference between the permethrin group and the standard-care group was not significant ($P=0.17$). The combined relative reduction in the two groups that underwent mass drug administration was 62% (95% CI, 49 to 74).

At 12 months, the rate of the appearance of scabies was lowest in the ivermectin group (1.3%), and the rate of the disappearance of scabies was highest in this group (97.3%) (Table 3). The prevalence of scabies at 3 months was lower than the prevalence at baseline in all groups: 13.9% (95% CI, 9.2 to 20.5) in the ivermectin group, 22.2% (95% CI, 15.4 to 30.9) in the permethrin group, and 10.4% (95% CI, 6.7 to 16.1) in the standard-care group. The one participant with crusted scabies had been clinically cured by the time of the 3-month visit. In all the groups, the number of routine clinic consultations for skin disease was lower in the period after the intervention than in the period before the intervention, with 10.6 fewer consultations per 100 baseline population per year in the ivermectin group, 7.0 fewer in the permethrin group, and 13.7 fewer in the standard-care group (Table S7 in the Supplementary Appendix).

ADVERSE EVENTS

Adverse events were more common in the ivermectin group than in the permethrin group (with 15.6% having an event and 205 events in 112 participants vs. 6.8% having an event and 46 events in 36 participants) (Tables S8 and S9 in the Supplementary Appendix). No adverse event was serious or persisted for more than 7 days. Itching was the most common event (affecting 5.3% and 3.6% of participants in the ivermectin and permethrin groups, respectively), followed by headache (affecting 3.8% and 0.9%, respectively).

DISCUSSION

In this comparative trial, we found significant reductions in the prevalence of both scabies and impetigo from baseline to 1 year in all groups, with by far the largest reduction in the ivermectin group. Adverse events were more common in the ivermectin group, but all events were mild and resolved quickly.

Mass drug administration shows promise as an important control strategy in countries in which scabies is endemic. Previous single-group studies of the mass administration of permethrin and of ivermectin have shown reductions in disease prevalence[6-8,20,32] but have not determined whether this strategy is superior to an effective application of standard care.

In our study, the prevalence of scabies in the groups that underwent mass drug administration had declined by 3 months and declined further by 12 months; this finding was somewhat contrary to our expectation. A proportion

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of the scabies cases detected at 3 months may have represented postscabietic inflammatory nodules, which can persist after successful treatment.[26,33]

The relative reduction in the prevalence of scabies from baseline to 12 months was significantly greater in the ivermectin group than in the permethrin group (94% vs. 62%). During mass administration, any therapeutic advantage of permethrin[34] may be outweighed by poor adherence to the topical agent.[17] Administration of treatment was directly observed much more frequently in the ivermectin group than in the permethrin group (96% vs. 58%). The effect of adherence in the ivermectin group may have been enhanced by the second dose for participants with clinical scabies at baseline, since ivermectin is not effective against unhatched eggs.[35]

Adverse-event profiles were consistent with those in previous studies.[36] Itching was the most common event and was probably caused by an inflammatory response to dead mite antigens. The extensive mass administration of ivermectin in Africa and Latin America[24,37] has raised no safety concerns, except for a contraindication to the drug among persons at risk for *Loa loa* filariasis.[38] In the absence of data on safety in young children and pregnant women, caution dictates that the drug remain contraindicated in these two groups.

The considerable decline in the prevalence of scabies in the standard-care group may have occurred because the trial introduced a higher level of care than had been routinely available, including ensuring the availability of permethrin and generating greater awareness about treatment for contacts.

This study has several limitations. A true cluster-randomized trial would have required multiple communities to be included in each group, but this trial design was beyond the resources available to us. We targeted a very substantial level of effect to minimize the possibility that any finding would be interpreted as being a result of confounding. There were nevertheless differences among the three trial communities, with respect to population movement and isolation from the main island of Viti Levu (Fig. 1). The standard-care group had access to private boats to the main island, and the permethrin group had easier access to the mainland by ferry than did the ivermectin group. These differences were reflected in the reported movements of study participants and may have contributed to a greater potential for reinfestation in the standard-care and permethrin groups than in the ivermectin group. Finally, the high prevalences of scabies and impetigo at baseline were consistent with findings from earlier surveys in the Pacific Islands.[39] We used validated diagnostic criteria[13] but not dermatoscopy, since this type of examination was not practical to perform and has poor sensitivity.[40,41] The study nurse who performed all skin examinations had worked at the only dermatology hospital in Fiji for more than 20 years and had had particular experience in the detection of scabies and impetigo. We did not systematically examine breasts and genitals, which are regions with a predilection for infestation,[19,42] but any resulting underestimation is unlikely to have differed among the three groups.

These data support the mass administration of ivermectin for scabies control. Although scabies resistance has been reported very infrequently, it could occur.[43,44] We provided a second dose for participants who had scabies at baseline, but a simpler strategy for mass administration on a larger scale would be to provide two directly observed doses 7 to 14 days apart, regardless of whether clinical scabies is present. There is an opportunity to evaluate the effect of existing ivermectin-based programs for onchocerciasis and lymphatic filariasis on scabies and other ivermectin-susceptible parasites. In general, approaches to mass drug administration may yield better results if they are integrated across diseases in a way that is acceptable to individual persons and communities.

SHIFT fills an important gap in evidence for scabies control, but effectiveness must now be evaluated beyond island settings and in larger populations. Key issues will include the number of cycles needed; the model of delivery; the mechanism for evaluation of efficacy, cost effectiveness, and acceptability; and the effect of scabies and impetigo control on the severe downstream complications of these skin conditions.[45]

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