Prevention of bacterial complications of scabies using mass drug administration: A population-based, before-after trial in Fiji, 2018–2020

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Summary

Background Scabies is an important predisposing factor of impetigo which can lead to serious bacterial complications. Ivermectin-based mass drug administration can substantially reduce scabies and impetigo prevalence in endemic settings, but the impact on serious bacterial complications is not known.

Methods We conducted a before-after trial in the Northern Division of Fiji (population: 131,914) of mass drug administration for scabies control. Prospective surveillance was conducted from 2018 to 2020. Mass drug administration took place in 2019, involving two doses of oral ivermectin or topical permethrin, delivered alongside diethylcarbamazine and albendazole for lymphatic filariasis. The primary outcomes were incidence of hospitalisations with skin and soft tissue infections, and childhood invasive infections and post-streptococcal sequelae. Secondary outcomes included presentations to primary healthcare with skin infections and community prevalence of scabies and impetigo.

Findings The incidence of hospitalisations with skin and soft tissue infections was 17% lower after the intervention compared to baseline (388 vs 467 per 100,000 person-years; incidence rate ratio 0.83, 95% CI, 0.74 to 0.94; $P = 0.002$). There was no difference in incidence of childhood invasive infections and post-streptococcal sequelae. Incidence of primary healthcare presentations with scabies and skin infections was 21% lower (89.2 vs 108 per 1000 person-years, incidence rate ratio, IRR 0.79, 95% CI, 0.78 to 0.82). Crude community prevalence of scabies declined from 14.2% to 7.7% (cluster-adjusted prevalence 12.5% to 8.9%; prevalence ratio 0.71, 95% CI, 0.28 to 1.17). Cluster-adjusted prevalence of impetigo declined from 15.3% to 6.1% (prevalence ratio 0.4, 95% CI, 0.18 to 0.86).

Interpretation Mass drug administration for scabies control was associated with a substantial reduction in hospitalisations for skin and soft tissue infections.

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Keywords: Impetigo; Ivermectin; Mass drug administration; Scabies; Skin and soft tissue infections

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Research in context

Evidence before this study

We searched PubMed for publications in English from database inception until January 31, 2021, using search terms including but not limited to "mass drug administration", "scabies", "impetigo", "skin and soft tissue infections", "sepsis", "glomerulonephritis" and "rheumatic heart disease". A series of trials conducted mainly in Pacific island countries have demonstrated that ivermectin-based mass drug administration for scabies leads to substantial reductions in the prevalence of scabies with concomitant reductions in the prevalence of impetigo. A study in Fiji published in 2015 found that ivermectin-based mass drug administration achieved a reduction in scabies prevalence by 94% and impetigo prevalence by 67% when measured one year after the intervention. A larger study of co-administration of azithromycin and ivermectin mass drug administration in the Solomon Islands published in 2019 demonstrated similar findings. A study of a community-based programme of scabies control in the Solomon Islands using ivermectin published in 2005 observed a reduction in haematuria among children, concomitant with reductions scabies and impetigo prevalence, suggesting a potential impact on kidney disease. A study in Tanzania published in 2012 observed a reduction in primary health care presentations for scabies treatment over a five year period of annual mass drug administration of ivermectin and albendazole for control of lymphatic filariasis. We found no studies that measured the impact of mass drug administration for scabies on hospitalisation for potential complications of scabies.

Added value of this study

This is the largest reported study of ivermectin-based mass drug administration for scabies, with delivery of treatment to a study population of 132,000 people. The study demonstrated significant reductions in the incidence of hospitalizations and primary health presentations for bacterial skin and soft tissue infections. There was no change in the incidence of hospitalization for invasive infections or post-streptococcal sequelae. Reductions in community prevalence of scabies and impetigo were observed 12 months after the intervention. This study demonstrates that reductions in healthcare presentations for the bacterial complications of scabies can be achieved through ivermectin-based mass drug administration.

Implications of all the available evidence

This study provides further evidence to support scabies control using mass drug administration in endemic settings. Previous studies have consistently demonstrated that ivermectin-based mass drug administration leads to substantial reductions in community prevalence of scabies and impetigo, and now this study shows that this benefit extends to reducing hospitalisation and primary health care presentations for the complications of scabies, namely more severe bacterial skin and soft tissue infections. Further research is needed to determine the effectiveness of this intervention when implemented in non-island and larger scale settings, and to determine the cost-effectiveness of this intervention to aid policy decision-making.

Introduction

Scabies is a skin disease caused by the mite *Sarcoptes scabiei* var. *hominis*. Scabies causes debilitating itch and sleep deprivation with socioeconomic consequences such as stigma, missed school or work, and substantial healthcare utilization.[1,2] An estimated 200 million people have scabies, predominantly in resource-poor settings,[3,4] contributing 0.21% of disability adjusted life-years from all diseases.[3]

Scabies leads to secondary bacterial skin infection when breaches in the skin enable bacteria to infiltrate the epidermis, with infection enhanced by mite serine protease inhibitors that impede the host's complement pathway and promote bacterial proliferation.[5] Most frequently, secondary infection presents as impetigo, which has an attributable risk from scabies estimated between 41 and 93% in endemic populations.[6,7] Impetigo, predominantly caused by *Staphylococcus aureus* and *Streptococcus pyogenes*, can lead to more severe skin and soft tissue infections (SSTI) as well as invasive infections and immune-mediated sequelae including post-streptococcal glomerulonephritis, and possibly acute rheumatic fever and rheumatic heart disease.[8–10]

Studies in Fiji and the Solomon Islands have demonstrated that ivermectin-based mass drug administration is effective in reducing community prevalence of endemic scabies by around 90%, with a concomitant reduction in impetigo prevalence of around 70%.[10–13] These studies did not detect any concerning safety signals, consistent with the extensive experience of ivermectin-based mass drug administration for control of lymphatic filariasis and onchocerciasis.[14]

The World Health Organization recognises scabies as a neglected tropical disease,[15] and in 2020, published a report of its first informal expert consultation on scabies control.[16] The consultation identified high priority research questions, including whether community-wide interventions for scabies have an effect on serious bacterial infections.[16]

We report the world's first study explicitly designed to investigate the impact of ivermectin-based mass drug administration for scabies on the occurrence of serious bacterial conditions. The intervention was delivered as part of an integrated mass drug administration program for the control of scabies and lymphatic filariasis.

Methods

Design and oversight

The Big Skin Health Intervention Fiji Trial ("Big SHIFT") was a before-after intervention trial of

ivermectin-based mass drug administration delivered to the whole population of the Northern Division of Fiji (census population 131,914 in 2017).[17] Outcomes were compared between the periods before and after the intervention, and focussed on bacterial infections.

Ethical approval was granted by the Fiji National Health Research and Ethics Review Committee (reference: 2018.38.NOR) and the Royal Children's Hospital Human Research Ethics Committee, Melbourne, Australia (reference: 38020). Verbal consent from those aged 18 years and older, and from the parents or guardians of those younger than 18 years was required to receive treatment in the mass drug administration program. Written third party consent was obtained from guardians for students dosed at school. Written informed consent was required from all participants in hospital surveillance and community prevalence surveys. The study was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12618000461291).

Setting

The Republic of Fiji is an archipelago nation with a tropical climate in the South Pacific Ocean spanning over 330 islands. Its national population of 884,887 people in 2017, consists mainly of two ethnicities - iTaukei or Indigenous Fijian (56.8%) and Fijians of Indian descent (37.5%).[17] The median age for both sexes is 27 years and the average life expectancy at birth in 2016 was 71 years for females and 66 years for males.[17,18] In 2018, Fiji's gross national income per capita was USD 5860.[19] Fiji was ranked at 93 of 187 countries on the United Nations Human Development Index in 2020.[20]

The study was set in the Northern Division of Fiji,[17] one of Fiji's four primary administrative units (Figure 1). The Northern Division is further divided into four administrative subdivisions - Macuata, Cakaudrove, Bua and Taveuni. The majority of the population (70.6%) live in rural settings, and 20% live in the division's capital, Labasa, located in Macuata subdivision and the only substantial urban centre.[17] According to a national survey in 2007, the Northern Division had the highest divisional prevalence of scabies (28.5%) and impetigo (23.7%) in Fiji.[17]

Intervention

Mass drug administration was conducted over six weeks, from 1 July to 11 August 2019, in collaboration

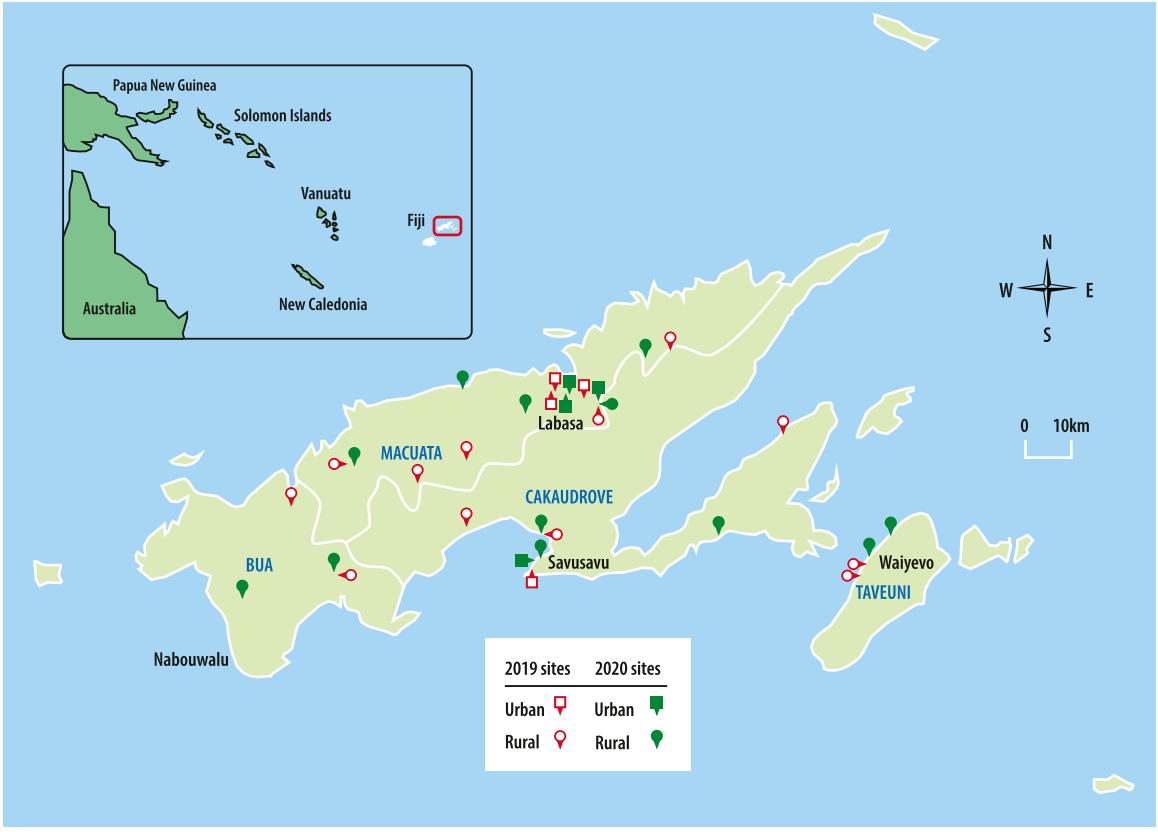

Figure 1. The Northern Division of Fiji with scabies prevalence survey sites indicated (inset map shows location of Fiji and the Northern Division in the Pacific region).

with the Fiji Ministry of Health and Medical Services as part of an integrated program for control of scabies and lymphatic filariasis. The study population was offered a first dose of ivermectin, diethylcarbamazine and albendazole as recommended for lymphatic filariasis mass drug administration,[21] followed by a second dose of ivermectin after 7 to 14 days. Dosage of ivermectin and diethylcarbamazine were administered according to height.[22] One 400 mg tablet of albendazole was given as a standard dose. Permethrin cream 5% was offered as two doses separated by 7 to 14 days to individuals for whom ivermectin was contraindicated - that is, those aged less than two years old, of a height less than 90 cm, pregnant or potentially pregnant, breastfeeding an infant aged less than 7 days old, taking warfarin or severely ill. The first dose of ivermectin was supplied by the Mectizan Donation Program. Ivermectin for the second dose (product name: IverP, manufactured by Fundación Mundo Sano, Argentina) and permethrin cream (product name: Glenper, manufactured by Glemark, India) were procured through research funding.

Distribution of drugs was achieved through visits to households, schools and workplaces by zone nurses, community health workers and other health cadres. Population awareness and sensitization to the distribution program were achieved through mass media and community-based measures conducted prior to and during distribution.

Primary outcome

The two primary outcomes were to evaluate the impact of ivermectin-based mass drug administration on: (1) hospitalisations with bacterial SSTIs; and (2) hospitalisations with scabies-related serious bacterial infections that were not SSTIs among those aged less than 15 years (defined below). The baseline period of surveillance was 48 weeks from July 2018 to June 2019 and the post-intervention period was 50 weeks from August 2019 to July 2020.

Primary outcomes were recorded through active surveillance of hospitalisations at the referral hospital of the Northern Division, Labasa Hospital by the study team. Study nurses performed daily visits to the hospital. Inpatients potentially meeting study criteria were identified using multiple processes to ensure comprehensive and accurate recruitment. First, study nurses reviewed admission registries in each ward and the clinical notes of new admissions. Second, they consulted with the nursing manager of each ward. Third, microbiology laboratory logs were reviewed for relevant isolates, which were traced back to the patient for potential recruitment. Study nurses were not involved in the clinical care of the participants and hence could not influence the diagnosis of the patients. We defined a bacterial SSTI as: clinically diagnosed impetigo, abscess, cellulitis, pyomyositis, necrotizing fasciitis (with pure growth of *S. aureus* or *S. pyogenes*) and infected scabies.[23] We defined scabies-related, non-SSTI serious bacterial diseases as invasive *S. aureus* or *S. pyogenes* infection, post-streptococcal glomerulonephritis, acute rheumatic fever or rheumatic heart disease. Invasive bacterial infection was defined by laboratory-confirmed isolation of *S. aureus* or *S. pyogenes* from a normally sterile site.[24,25] Post-streptococcal glomerulonephritis, acute rheumatic fever and rheumatic heart disease were defined according to published criteria.[26,27]

Quarterly reviews for missed cases were conducted by the local study coordinator or data manager by reviewing ward registries, microbiology laboratory records and the digital patient information system (known as PATIS).[28] If a missed case was found, consent was sought for enrolment from the patient via home visit or phone. If informed consent was not possible, the admission was recorded for incidence calculations only. Checks for accuracy were also performed quarterly; data entered into REDCap for complete entries were compared to the patient medical records and corrections made and documented accordingly.

Secondary outcomes

Secondary outcomes were to evaluate the impact of ivermectin-based mass drug administration on: (1) hospitalisations with scabies-related non-SSTI serious bacterial diseases for all ages; (2) presentations to primary healthcare facilities for scabies or SSTI[29]; and (3) community prevalence of scabies and impetigo.

Surveillance for hospitalisations took place over the same period and used the same mechanism described for the primary outcome. Surveillance for scabies and SSTIs at primary healthcare facilities was carried out over 50 weeks at baseline from July 2018 to June 2019 and the post intervention period was 51 weeks from August 2019 to July 2020. Presentations with scabies and bacterial SSTIs (defined as infected scabies, impetigo, abscess, cellulitis and severe skin infection) were recorded using a monthly reporting system established at all 42 public primary care facilities in the Northern Division. De-identified data listing patient diagnosis, demographics and treatment for individual presentations were recorded by clinicians from each facility in a study booklet. Most clinicians transcribed these data from their patient registries monthly or recorded them directly case-by-case into the study booklet. Sheets from the study booklet were forwarded to the study team monthly, and data entered into a REDCap database, securely stored in an online server housed at MCRI.[30,31] Cases recorded to have both abscesses and cellulitis were counted as abscess only, on the assumption that the cellulitis was associated with the abscess. Cases recorded to have both scabies and impetigo were analysed as having scabies, impetigo and infected scabies.[29,32]

Community prevalence of scabies and impetigo was measured just prior to mass drug administration (May 2019) and 12 months after (July 2020). At each survey, 16 communities were randomly chosen from those with a population between 50 and 400, with probability of selection proportionate to size after stratification within the four subdivisions and accounting for urban-rural location.[33] Clinical examinations were conducted by nurses trained by the study team for the presence and severity of scabies and impetigo using previously defined criteria.[11,34]

Treatment coverage. Each dose of mass drug administration given was recorded in a coverage booklet by mass drug administration distributors. Coverage for each community was compiled from these booklets into a coverage summary form by zone nurses, and community profile data from the Ministry of Health and Medical Services were used for denominators when calculating treatment coverage. The number of doses given as recorded in the coverage summary form was divided over the total population from the community profile data to calculate coverage for communities, subdivision and the entire Northern Division. The total population of the Northern Division according to these profiles was 139,977, differing slightly from the census figures. No age breakdown was available from the community profiles for age-specific reporting.

Safety

Serious adverse events, as defined by the WHO,[35] that occurred within 24 h of treatment, were reported by the treating clinician to the Principal Study Coordinator and subsequently to the study Data Safety Monitoring Board and to the Fiji Centre for Communicable Disease Control. Inadvertent consumption of ivermectin during pregnancy was reported by treating clinicians and outcomes of the pregnancy followed up by the study. Clinician representatives from all health facilities were trained in these reporting processes prior to the mass drug administration.

Statistical analysis

We calculated incidence of outcomes using population denominators from the 2017 Fiji Bureau of Statistics census.[17] Incidence was expressed per 100,000 population per year for hospitalisations and per 1000 for primary healthcare presentations. Hospitalisations and primary health presentations that occurred during the six weeks of mass drug administration were excluded from incidence calculations. Disease-specific incidence was calculated for hospitalisations and primary health presentations using previously described methods.[23,29] Incidence for conditions monitored through hospitalisations was annualised for both the baseline period (48 weeks of observation) and the post-intervention period (50 weeks). Similarly, incidence was annualised for primary health care presentations for the baseline and post-intervention periods (50 weeks and 51 weeks, respectively).

We compared prevalence of scabies and impetigo at baseline and 12 months after mass drug administration using a statistical technique which adjusted for clustering effect.[33] We first calculated prevalence of scabies and impetigo in each cluster (community) separately, and then these cluster-level summaries were analysed using a paired t-test to estimate 95% confidence intervals (CI) for the corresponding prevalence ratios to test our null hypothesis of no effect of mass drug administration. Analysis was performed using Stata 14.0 (CS, Texas, USA).

Based on existing routinely collected data and our previous studies,[11,12,24,27] we anticipated that the baseline incidence of hospitalisations with SSTI would be 293 per 100,000 population, and 123 per 100,000 population for scabies-related non-SSTI serious bacterial diseases among those aged less than 15 years. We calculated that we would have approximately 90% power to detect a 50% reduction in SSTI hospitalisations, and 80% power to detect a 40% reduction in non-SSTI serious bacterial infections among those aged less than 15 years.

Role of the funding source

Funding for the study was provided by the Australian National Health and Medical Research Council through a Project Grant (GNT1127300) and Centre for Research Excellence (GNT1153727) and the Scobie and Claire Mackinnon Trust. None of the funding sources had any involvement in data collection, analysis, or interpretation; trial design; patient recruitment; or any aspect pertinent to the study. None of the funders had any role in the writing of the manuscript or the decision to submit it for publication.

Results

The first treatment dose was received by 135,744 people (97% coverage) and the second treatment dose by 121,760 people (87%; Supplementary Appendix).

Primary outcome

There were 493 hospitalisations with SSTIs after the intervention (incidence 388.7 per 100,000) compared to 569 (467.3 per 100,000 person years) during the baseline period, representing a 17% reduction (incidence rate ratio, IRR 0.83; 95% CI, 0.74 to 0.94; $P = 0.002$; Table 1). The greatest reduction in SSTI hospitalisations was found among those aged 25–34 years (0.50; 95% CI, 0.32 to 0.75, $P = 0.0005$; Supplementary Appendix). There was no reduction found among those aged over 64 years. Incidence of SSTIs hospitalisations arising from Macuata subdivision alone was 689.6

	Period before mass drug administration		Period after mass drug administration		Comparison	
	n	Incidence per 100,000 (95% CI)	*n*	Incidence per 100,00 (95% CI)	Incidence rate ratio (95% CI)	*P*
Abscess	398	326.9 (296.3–360.5)	331	261 (234.3–290.6)	0.8 (0.7–0.92)	0.0018
Cellulitis	106	87.1 (92–105.3)	113	89.1 (74.1–107.1)	1.04 (0.79–1.35)	0.7934
Pyomyositis	27	22.2 (15.2–32.3)	22	17.3 (11.4–26.3)	0.76 (0.41–1.37)	0.3317
Infected scabies	27	22.2 (15.2–32.3)	14	11 (6.5–18.6)	0.48 (0.24–0.94)	0.0226
Impetigo	8	6.6 (3.3–13.1)	6	4.7 (2.1–10.5)	0.67 (0.2–2.1)	0.4545
Necrotizing fasciitis	2	1.7 (0.2–5.9)	5	3.9 (1.3–9.2)	2.4 (0.4–26.3)	0.2153
Total	568	466.5 (429–506.4)	491	387.1 (353.7– 422.8)	0.83 (0.73–0.94)	0.0024

***Table 1*: Hospitalisations with skin and soft tissue infections before and after mass drug administration.**

(95% CI 625.4–758.6) at baseline, falling to 575.3 (95% CI 518–637.3, IRR 0.87, 95% CI 0.86–0.88) after the intervention. There were 36 hospitalisations with non-SSTI serious bacterial infections among those aged less than 15 years after the intervention, compared with 36 during the baseline period (IRR 0.95; 95% CI, 0.59 to 1.53; $P = 0.82$; Table 2).

Secondary outcomes

There was no difference in the incidence of hospitalisations with serious non-SSTI infections between the baseline and post intervention periods for all ages (Supplementary Appendix).

There were 11,151 individual presentations to primary healthcare facilities after the intervention (incidence 89.2 per 1000) compared with 13,736 in the period prior (108.3 per 1000 person-years), representing a 21% reduction (IRR 0.79; 95% CI, 0.78 to 0.82; Table 3). The incidence of bacterial SSTIs declined by 15% (IRR 0.85; 95% CI 0.83 to 0.88) from 89.2 per 100,00 to 76.3 per 100,000. Presentations for scabies declined by 50%. Presentations to facilities servicing urban catchments declined by 39% from 4064 presentations (82.5 per 1000) to 2518 presentations (50.1 per 1000; IRR 0.61; 95% CI, 0.58 to 0.64), while presentations to rural facilities declined by 12% (IRR 0.88; 95% CI, 0.85–0.9; Supplementary Appendix).

At the baseline community survey, 476 of 3365 participants had scabies (crude prevalence 14.2%), and 12 months after the intervention, 327 of 4252 participants had scabies (7.7%), representing a 46% reduction in the unadjusted analysis (prevalence ratio 0.54; 95% CI, 0.48 to 0.62, $P < 0.001$; Table 4 and Supplementary Appendix), and a 29% reduction in the cluster-adjusted analysis (prevalence ratio 0.71; 95% CI, 0.28 to 1.17, $P = 0.144$; Table 4). There was a significant reduction in the prevalence of moderate to severe scabies (prevalence ratio 0.48; 95% CI 0.25 to 0.91, $P = 0.044$). The cluster-adjusted prevalence of impetigo declined from 15.3% to 6.1% (prevalence ratio 0.4; 95% CI 0.18 to 0.86, $P = 0.021$). There was a greater reduction in the prevalence of scabies in urban communities (from 14.4% to 3.3%) compared to rural communities (from 14% to 10%). Impetigo prevalence also reduced more markedly in urban communities compared to rural (Supplementary Appendix).

Safety

There were two serious adverse events reported during the period of mass drug administration. One participant experienced a delayed hypersensitivity reaction and the other developed chest pain. Both occurred a few hours after administration of ivermectin, diethylcarbamazine and albendazole and required hospitalisation for observation.

	Period before mass drug administration		Period after mass drug administration		Comparison
	n	Incidence per 100,000 (95%CI)	*n*	Incidence per 100,000 (95%CI)	Incidence rate ratio (95% CI)
Invasive *Staphylococcus aureus*	22	18.1 (11.3–27.4)	16	12.6 (7.2–20.5)	0.7 (0.3–1.4)
Rheumatic heart disease	6	4.9 (1.8–10.7)	10	7.9 (3.8–14.5)	1.6 (0.5–5.4)
Invasive *Streptococcus pyogenes*	3	2.4 (0.5–7.2)	5	3.9 (1.3–9.2)	1.6 (0.3–10.3)
Post streptococcal glomerulonephritis	4	3.3 (0.9–8.4)	1	0.8 (0.02–4.4)	0.2 (0.005–2.4)
Acute rheumatic fever	1	0.82 (0.02–4.6)	5	3.9 (1.3–9.2)	4.8 (0.5–227)
Total	36	92.9 (67–128.8)	36	89.2 (64.4–123.6)	0.95 (0.6–1.5)

***Table 2*: Hospitalisations among people aged less than 15 years with serious, non-skin and soft tissue infections.**

Condition	Period before mass drug administration		Period after mass drug administration		Comparison
	n	Incidence per 1000 (95%CI)	*n*	Incidence per 1000 (95%CI)	Incidence rate ratio (95% CI)
Abscess	8052	63.5 (62.1−−64.8)	7709	59.6 (58.3−60.9)	0.94 (0.67−0.91)
Scabies	3643	28.7 (27.8−29.7)	1870	14.5 (13.8−15.1)	0.5 (0.48−0.53)
Impetigo	2738	21.6 (20.8−22.4)	1687	13 (12.4−13.7)	0.6 (0.57−0.64)
Infected scabies	1133	8.9 (8.4−9.5)	551	4.3 (3.9−4.6)	0.48 (0.43−0.53)
Cellulitis	416	3.3 (3−3.6)	410	3.2 (2.9−3.5)	0.97 (0.84−1.11)
Severe skin infection	186	1.5 (1.3−1.7)	105	0.8 (0.7−1)	0.55 (0.43−0.71)
Total*	13736	108.3 (106.6−110)	11151	86.2 (84.7−87.7)	0.79 (0.78−0.82)

***Table 3*: Primary healthcare presentations with scabies and skin and soft tissue infections. (*individuals may have had more than one condition at presentation; the total refers to the number of people presenting and so is less than the sum of the rows above).**

	Baseline (16 clusters)		12 months (16 clusters)		Comparison	
	n/N	% (95% CI)	n/N	% (95% CI)	Cluster-adjusted prevalence ratio (95% CI)	*P*
Scabies	476/3365	12.5 (8.5−16.5)	327/4252	8.9 (5.6−12.2)	0.71 (0.28−1.17)	0.144
Moderate-severe scabies	161/3365	4.4 (2.0−6.7)	88/4252	2.1 (1.3−3.0)	0.48 (0.25−0.91)	0.044
Impetigo	148/882*	15.3 (5.6−25.0)	236/4252	6.1 (2.8−9.4)	0.4 (0.18−0.86)	0.021

***Table 4*: Cluster-adjusted prevalence of scabies and impetigo at baseline and 12 months after mass drug administration (*impetigo prevalence was measured in 9 clusters at baseline).**

One pregnant woman at week five of gestation ingested ivermectin, diethylcarbamazine and albendazole. The infant was born with a diaphragmatic hernia, requiring surgical repair shortly after birth, and survived.

Discussion

In this first ever investigation of the impact of ivermectin-based mass drug administration for scabies control of serious bacterial infection, we observed a 17% reduction in the incidence of hospitalisation with bacterial SSTIs. While no change in the incidence of serious non-SSTI diseases was found, our primary findings are supported by demonstration of a 21% reduction in the incidence of primary healthcare presentations with SSTIs as well as reductions in scabies and impetigo prevalence at the community level. The intervention was safe with minimal severe adverse events.

In this population of approximately 140,000 people, the intervention was associated with a reduction in the number of hospitalisations and primary health care presentations for scabies and SSTIs per year by nearly 80 and over 2000, respectively. Our findings lend further support to a mass drug administration approach for scabies control in endemic communities, and to the strategy outlined by the WHO informal consultation framework for scabies control.[16]

The reduction in hospitalisations with SSTIs was lower than we estimated in our sample size calculations. A possible reason is that we did not observe as great a reduction in scabies prevalence as in previous studies of mass drug administration for scabies.[11,12,36,37] Potential reasons for this are the scale of implementation (study population approximately six times larger than previous trials) and the real-world programmatic approach to treatment distribution. The mass drug administration campaign was not distributed and overseen directly by the study team as would have been done in earlier trials. Furthermore, the Northern Division is less remote compared to the locations of previous mass drug administration studies, and so population mobility was greater and reintroduction of scabies from new arrivals more frequent. While the incidence of invasive *S. aureus* and *S. pyogenes* infections was high compared to high-income settings,[8,38,39] hospitalisations for rheumatic fever and post-streptococcal glomerulonephritis were infrequent, and the lower-than-expected baseline incidence potentially limited our ability to detect a significant change.

We used a before-after study design for pragmatic reasons, and therefore normal fluctuations in incidence and other confounders may have influenced the results. Modelling for baseline fluctuations over time was not possible as data from only the two time periods of observation were available. The consistency of reductions in scabies and impetigo prevalence with reductions in hospitalisations and primary healthcare presentations support the hypothesis that these changes were a result of the intervention. A cluster randomised trial design would require at least 10 geographically separated units of randomisation, each with very large population sizes,[33] which would not be feasible in Fiji or many other settings. We suggest that as programs for scabies

control are implemented at scale, the impact on the bacterial complications of scabies is evaluated.[16]

We measured the impact of the program after a single round of treatment.[40,41] The WHO informal consultation framework recommends three to five rounds, reflecting the translation of results from carefully conducted trials on small islands to the wider world.[16] It is possible that with more than one round of mass drug administration, an even greater impact on the bacterial complications of scabies could be realised. This study is the first to include urban areas in an evaluation of the effectiveness of mass drug administration for scabies. We observed greater reductions in primary care presentations and community prevalence in urban areas compared to rural. Further research is needed to better understand factors associated with reduction in scabies and SSTIs following large-scale mass drug administration including coverage, impact of seasonal migration, accessibility of healthcare services and water, sanitation and hygiene conditions. Further research is also needed to evaluate the health-economic benefits of mass drug administration for scabies.[16] An important consideration regarding cost-effectiveness is the ability to integrate scabies programs with programs for other neglected tropical diseases.[16]

Our study achieved high coverage of 97% and 87% for first and second doses respectively, demonstrating the feasibility of integration of scabies control measures with mass drug administration for lymphatic filariasis. Coverage was measured at the time of mass drug administration using data from distributors and community profiles. Our coverage figures may have overestimated true coverage if the denominator were underestimated, for example if community profiles were not up to date, however we did not have a secondary method to verify our figures. All participants in the study also received diethylcarbamazine and albendazole as mass drug administration for lymphatic filariasis, however neither of these medications have activity against the scabies mite or bacterial pathogens. While lymphedema related to chronic lymphatic filariasis may be complicated by cellulitis, the prevalence of filarial infection is very low in the study population (1.08% in 2019) and clinically apparent cases rare.[42] It is therefore unlikely that mass drug administration treatment of such cases would have contributed to reductions we observed in the incidence of SSTIs. Furthermore, the mass drug administration campaign did not include any educational information on the care of chronic lymphatic filariasis and so there would be no additional impact on SSTI reductions by the campaign.

Our findings add to the emerging evidence base for mass drug administration for control of scabies, demonstrating the potential benefits of this intervention beyond reducing scabies and impetigo prevalence. More research is needed to support our findings including in non-island settings and after multiple rounds of mass drug administration.

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All authors confirm they had full access to all the data in the study and accept responsibility to submit for publication.

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Data sharing statement

De-identified, individual participant data including data dictionaries which underlie the results reported in this article (inclusive of text, tables, figures and appendices) will be made available immediately following publication, ending 5 years following article publication to anyone for any purpose. Proposals should be directed to the corresponding author.

Editor note

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Declaration of interests

None of the authors have any conflict of interest to declare.

Supplementary materials

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