Randomised trial of community treatment with azithromycin and ivermectin mass drug administration for control of scabies and impetigo

Michael Marks¹, Hilary Toloka³, Ciara Baker⁴, Christian Kositz¹, James Asugeni³, Elliot Puiahi⁵, Rowena Asugeni³, Kristy Azzopardi⁴, Jason Diau³, John M Kaldor⁶, Lucia Romani⁶, Michelle Redman-MacLaren⁷, David MacLaren⁷, Anthony W Solomon¹,², David CW Mabey¹,² and Andrew C Steer⁴,⁸,⁹

1 Clinical Research Department, Faculty of Infectious and Tropical Diseases, London School of Hygiene & Tropical Medicine, Keppel Street, London, WC1E 7HT, United Kingdom

2 Hospital for Tropical Diseases, University College London Hospitals NHS Trust, London, WC1E 6JB, United Kingdom

3 Atoifi Adventist Hospital, Atoifi, Malaita Province, Solomon Islands

4 Group A Streptococcal Research Group, Murdoch Children’s Research Institute, Melbourne, Victoria, Australia

5 National Referral Hospital, Honiara, Solomon Islands

6 Kirby Institute, University of New South Wales, Sydney, Australia

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7 College of Medicine and Dentistry, James Cook University, Cairns, Queensland, Australia

8 Centre for International Child Health, University of Melbourne, Melbourne, Victoria, Australia

9 Department of General Medicine, Royal Children’s Hospital, Melbourne, Victoria, Australia
Summary

Scabies is a major cause of impetigo. We assessed the effect on impetigo prevalence of adding azithromycin to ivermectin mass drug. The decrease in impetigo did not differ between communities treated with ivermectin and communities treated with ivermectin and azithromycin.

Registered on clinicaltrials.gov (NCT02775617).
Abstract

Background

Scabies is a public health problem in many countries, with impetigo and its complications important consequences. Ivermectin based mass drug administration (MDA) reduces the prevalence of scabies and, to a lesser extent, impetigo. We studied the impact of co-administering azithromycin on the prevalence of impetigo and antimicrobial resistance.

Methods

Six communities were randomised to receive either ivermectin-based MDA or ivermectin-based MDA co-administered with azithromycin. We measured scabies and impetigo prevalence at baseline and twelve months. We collected impetigo lesions swabs at baseline, three and twelve months to detect antimicrobial resistance.

Results

At baseline, scabies and impetigo prevalences were 11.8% and 10.1% in the ivermectin-only arm and 9.2% and 12.1% in the combined treatment arm. At twelve months, the prevalences had fallen to 1.0% and 2.5% in the ivermectin-only arm and 0.7% and 3.3% in the combined treatment arm. The proportion of impetigo lesions containing Staphylococcus aureus detected did not change (80% at baseline vs 86% at twelve months; no significant difference between arms) but the proportion containing pyogenic streptococci fell significantly (63% vs 23%, p < 0.01). At three months, 53% (8/15) of S. aureus isolates were macrolide-resistant in the combined treatment arm, but no resistant strains (0/13) were detected at twelve months.

Conclusions

Co-administration of azithromycin with ivermectin led to similar decreases in scabies and impetigo prevalence compared to ivermectin alone. The proportion of impetigo lesions
containing pyogenic streptococci declined following MDA. There was a transient increase in the proportion of macrolide-resistant *S. aureus* strains following azithromycin MDA.

**Key Words:** Scabies, Neglected tropical diseases, Ivermectin; Impetigo; Antimicrobial resistance
Background:

Scabies is a major public health problem in many tropical countries [1]. As well as the direct consequences of infestation, scabies leads to an increased risk of secondary bacterial skin disease (impetigo), mostly due to *Staphylococcus aureus* and *Streptococcus pyogenes*[2], due to breaks in the skin and possibly down-regulation of complement by *Sarcoptes scabei* [3]. Skin infections, especially those due to *S.pyogenes*, can result in more serious disease, including bacteraemia, glomerulonephritis and possibly rheumatic heart disease[1,4–6]. In 2017 scabies was formally recognised as a neglected tropical disease (NTD) by the World Health Organization (WHO), leading to increased interest in strategies for controlling scabies and its associated morbidity.

Mass drug administration (MDA) has been demonstrated to be effective as a control measure for scabies, through single-arm studies using permethrin or ivermectin [7–10] and, recently, a comparative trial Fiji which demonstrated ivermectin was superior to permethrin [11]. In these studies, community-wide treatment for scabies, without antibacterial therapy, led to substantial reductions in impetigo.

Given the ongoing burden of impetigo and its complications in these settings, it is reasonable to consider whether the addition of an antibacterial agent may be beneficial. The macrolide azithromycin is a potential candidate for this role, because it has good activity against *S. pyogenes* and *S. aureus*. Because of its long half-life and low toxicity, it is recommended by WHO for mass drug administration for control of trachoma, and eradication of yaws[12,13].

Any benefit from community-wide use of antimicrobial agents needs to be weighed against the risk of promoting the selection of antimicrobial resistant organisms. A number of studies have assessed the impact of azithromycin MDA on nasopharyngeal or oropharyngeal carriage of azithromycin resistant bacteria[14–18] but none have assessed the impact on organisms isolated from impetigo lesions.
As in many Pacific Island nations, the prevalence of scabies and impetigo is high in the Solomon Islands [7,19–21]. Yaws and trachoma have also been found at high levels in the Solomon Islands[22–24]. This co-endemicity has provided a rationale to consider co-administration of ivermectin and azithromycin. Previous studies suggest that co-administration is safe compared to individual use of the two agents [25,26].

We conducted a community randomised trial to assess whether adding azithromycin to ivermectin-based MDA for scabies had an additional impact on the prevalence of impetigo at twelve months or on antimicrobial resistance of Gram-positive bacteria isolated from impetigo lesions.
Methods:

Study Setting and Recruitment

This was a community randomised open label study conducted in Malaita province of the Solomon Islands. Six communities were randomised to one of two arms: an ivermectin arm or a combined-treatment arm. We selected communities that were isolated from each other to reduce contamination between the two study arms.

All residents living in selected communities were eligible to participate. Community engagement and education were conducted by the study team prior to commencement of the study. Written informed consent was obtained from adults and from the parent or guardian of children. Assent was also obtained from children who were able to provide it.

Data Collection

Study visits took place at three timepoints. At baseline, participants were seen for enrollment, initial data collection and treatment. At three months, we re-examined children (aged ≤13 years) in each community to allow for collection of swabs to monitor for antimicrobial resistance (see below); this age group was selected as they were anticipated to have the highest prevalence of impetigo. At the twelve-month follow-up visit, we again aimed to examine all participating residents in participating communities. Prior to visits at both baseline and twelve months, the study team conducted a village census. At baseline and twelve months, participants underwent a standardised examination by an experienced clinician (MM) with data recorded on the presence or absence of any skin lesions, their location and whether they were consistent with scabies, impetigo or another diagnosis. The clinical diagnosis of scabies was based on the morphology (burrows, papules, nodules, vesicles) and distribution of rash alongside the presence of pruritus or evidence of excoriation. Active impetigo was diagnosed on the basis of discrete papular, pustular or ulcerative lesions with associated erythema, crusting, bullae or frank pus [27]. The severity of scabies and impetigo was classified as previously described[19]. Data were collected directly into Android smartphones using the OpenDataKit software package[28].
Treatment

Treatment was offered to all participating members of the community and was directly observed by the study team. In the ivermectin arm we administered ivermectin MDA at baseline. In the combined treatment arm we co-administered ivermectin and azithromycin MDA at baseline. Ivermectin MDA consisted of a single oral dose of ivermectin (200μg/kg) determined by body weight. In individuals with a contra-indication to ivermectin (pregnancy, breast-feeding, weight <15kg) topical permethrin was offered instead. Individuals clinically diagnosed with scabies at baseline were offered a second dose of ivermectin (or second application of topical permethrin) at seven days. [11]. Azithromycin MDA consisted of a single oral dose of azithromycin (30mg/kg, max 2gm) determined by body weight [29,30]

Sample Collection and Analysis

To assess changes in antimicrobial resistance, we aimed to collect swabs from approximately 40 active impetigo lesions in children (12 years or less) per treatment arm at baseline (equivalent to approximately one third of our anticipated cases of impetigo at baseline). At three months, swabs were collected from all children with active impetigo. Finally, at twelve months we again aimed to collect swabs from all individuals with active impetigo. We collected swabs from a single lesion in each individual. A sterile cotton-tipped swab was rolled across pus or exudate from active impetigo lesions and placed inside a dry-transport tube, then shipped at ambient temperature within seven days [31]. Swabs were sent to the Murdoch Children’s Research Institute, Melbourne, Australia, where they were streaked onto horse blood agar plates and incubated at 37°C in 5% CO₂. Plates were reviewed at 24 hours and purity plating performed. Beta-hemolytic streptococcal colonies were grouped by latex agglutination (Pro-Lab Diagnostics, Richmond Hill, Canada). *Staphylococcus aureus* colonies were detected using a latex slide agglutination test (Oxoid, United Kingdom). Antimicrobial sensitivity testing was performed using VITEK 2 (bioMérieux Inc., Durham, NC). We inferred azithromycin resistance from the results of erythromycin sensitivity testing using breakpoints defined by the Clinical and Laboratory Standards Institute[32]. We report sensitivity results for (1) *S. aureus* and (2) pyogenic streptococci (groups A, C and G) collectively, including *S. pyogenes* (group A).

*Emm*-typing was performed according to the protocol specified by the Centers for Disease Control and Prevention (CDC) with minor modifications, as previously described[33]. *Emm*-clusters were deduced based on the *emm*-typing results [34].
Statistical Analysis

The study was designed to assess whether adding a single oral dose of azithromycin, alongside ivermectin, resulted in a decrease in the prevalence of impetigo at twelve months compared to treatment with ivermectin alone. We calculated the prevalence of scabies and impetigo in each study arm at baseline and twelve months. We calculated the absolute and relative reduction in scabies and impetigo prevalence between baseline and twelve months. We compared the change in prevalence, separately for scabies and impetigo, between study groups by calculating the ratio of the prevalence at baseline and twelve months for each group, and testing the hypothesis that these two ratios were equal[35].

Sample Size Calculations

We estimated the pre-MDA prevalence of scabies and impetigo to be approximately 15% and 25% respectively. Based on previous studies, we anticipated the prevalence of scabies would fall to 1% in both arms and the prevalence of impetigo would fall to 10% at twelve months in the ivermectin-only arm[11,19]. Assuming that in the combined-treatment arm impetigo prevalence fell to 5%, and loss-to-follow-up was 10%, we needed to enroll 635 individuals in each study arm to have 80% power to detect a difference between study arms as significant at the 0.05 level. As a secondary outcome we calculated the proportion of S. aureus and S. pyogenes isolates which were macrolide resistant in each arm at baseline, three months and twelve months. Statistical analysis was conducted in R 3.4.2 [36].

Ethics Approval

The study was approved by the London School of Hygiene & Tropical Medicine, the Solomon Islands National Health Ethics Committee and the Atoifi Adventist Hospital Ethics Committee. Azithromycin was provided by WHO (who purchased it from Medopharm (India)). Ivermectin was purchased from Merck Sharp and Dohme (Australia). Permethrin was purchased from Pharmatec (Fiji). At twelve months, all individuals in the ivermectin-only arm were offered azithromycin in line with WHO guidelines for the treatment of yaws[13]. The study was prospectively registered on clinicaltrials.gov (NCT02775617). All authors had access to study data and shared responsibility for the decision to submit for publication.
Results:

At baseline, 1,291 individuals (90.8% of the resident population in the six study communities) were examined and received treatment. At the twelve-month follow-up the resident population of the study communities had decreased to 1,255, of whom 1,083 individuals were examined (86.3%) (Table 1). Follow-up was lower in the ivermectin-only arm at twelve months (ivermectin-only 76.2% vs combined treatment arm 96.3%). Overall 46.6% of participants were male and the median age of participants was 25 years (IQR 11-47) (Table 1).

At baseline the prevalence of scabies was 11.8% (95% CI 9.4-14.6%) in the ivermectin-only arm and 9.2% (95% CI 7.1 – 11.7%) in the combined-treatment arm. The severity of scabies was similar in both arms; overall 77.8% of individuals had mild scabies, 20% had moderate scabies and 2.2% had severe scabies (data not shown). No cases of crusted scabies were detected. At baseline the prevalence of active impetigo was 10.1% (95% CI 8.1 – 13.0%) in the ivermectin-only treatment arm and 12.1% (95% CI 9.7 – 14.9%) in the combined-treatment arm. The severity of impetigo was similar in both groups; overall 84.1% of participants had mild impetigo, 11% had moderate impetigo and 4.9% had severe impetigo (data not shown).

At twelve months the prevalence of scabies and impetigo had fallen to 1.0% (95% CI 0.3-2.6%) and 2.5% (95% CI 1.4 – 4.5%), respectively, in the ivermectin-only treatment arm and to 0.7% (95% CI 0.2 -1.8%) and 3.3% (95% CI 2.1 – 5.1%), respectively, in the combined treatment arms (Table 2). There was no significant difference between the two groups (91.5% vs 92.4%, p = 0.31), in the change from baseline to twelve months in scabies prevalence or the change in impetigo prevalence (75.2% vs 72.7%, p = 0.49).

We performed a post-hoc sensitivity analysis to assess whether the lower follow-up in the ivermectin-only arm might have affected our results. We calculated the prevalence of impetigo that would have been seen in the ivermectin-only treatment arm if we had achieved a follow-up at a level similar to the combined treatment arm and the prevalence amongst participants not seen at twelve months had been unchanged from baseline. Under
these assumptions, the prevalence of impetigo in the ivermectin-only treatment arm would have been 4.1% at twelve months. In this analysis there was no significant difference in the relative reduction in impetigo between arms (60.2% vs 72.7%, p = 0.23).

Swabs were collected from 73 people with impetigo at baseline, 36 people at three months, and 22 people at twelve months. At baseline, 80% of impetigo lesions from which we obtained a swab yielded *S. aureus* on culture and 62% yielded pyogenic streptococci (predominantly *S. pyogenes*, 56%). At three and twelve months the proportion of *S. aureus* was unchanged (78% and 86% respectively) but the proportion of impetigo lesions from which *S. pyogenes* were cultured had fallen significantly to 33% at 3 months (p = 0.04 for the comparison to baseline) and 23% at twelve months (p < 0.01 for the comparison to baseline). The relative decrease in *S. pyogenes* was similar in both arms of the study (Tables 3).

No macrolide resistance was detected among streptococci in either arm at any of the three time points. In the ivermectin-only treatment arm we did not isolate any macrolide-resistant *S. aureus* at any time point. In the combined-treatment arm, one isolate of *S. aureus* was macrolide-resistant at baseline, and 8/15 (53%) of *S. aureus* isolates were macrolide-resistant at three months. At twelve months, no macrolide-resistance was detected in any of the 6 isolates tested (Table 4). Isolates of *S. pyogenes* fell into 27 different *emm*-types. Twenty-five *emm*-types could be categorised into one of 11 different *emm*-clusters (Supplementary Table 1).
Conclusion:

In the first study to directly compare co-administration of azithromycin and ivermectin with ivermectin-only MDA, co-administration did not result in a greater decrease in the clinical prevalence of impetigo at twelve months, compared to ivermectin alone. Substantial decreases were observed in both the prevalence of scabies and impetigo, but the magnitude of the decrease was similar in the two study arms and consistent with the effect size seen in previous studies[11]. In both arms, we observed a large reduction in the proportion of impetigo lesions from which pyogenic streptococci were isolated, while the proportion of lesions from which S. aureus was cultured did not change in either arm.

A major aim of scabies control programmes is a reduction in sequelae of S. pyogenes infection. Our study provides some of the first data demonstrating that the observed reduction in clinical impetigo may be due to a reduction in S. pyogenes infection. This decrease in pyogenic streptococci occurred in both communities that received ivermectin alone and those in which it was co-administered with azithromycin. Why S. pyogenes should decline to a greater extent than S. aureus is unclear. Asymptomatic carriage of S. aureus is more common than carriage of S.pyogenes, and can persist following MDA with azithromycin[17], so might serve as a potential reservoir for ongoing transmission. Our data do not allow us to assess this hypothesis, and future studies to better understand the impact of MDA on impetigo lesions are warranted.

We observed an increase at three months in the proportion of strains of S. aureus that were macrolide resistant following MDA with azithromycin. This effect appeared to wane by twelve months post-MDA, although our sample size was too small to draw a firm conclusion on the duration of the effect. In the communities studied, there is limited use of macrolides other than in the management of sexually transmitted infections. The lack of ongoing selective pressure may have contributed to the return to a wild-type antibiotic susceptibility pattern at twelve months. Previous studies have demonstrated transient increases in the nasopharyngeal carriage of azithromycin resistant Streptococcus pneumoniae following azithromycin MDA, with limited evidence that multiple rounds of MDA lead to greater selection of resistant isolates than a single round [14–16]. A study of nasopharyngeal
carriage of *S. aureus* found macrolide resistance increased within a month of azithromycin MDA but then declined over six months. Individuals who received multiple rounds of MDA were more likely to have resistant strains than those who had received only one round[17]. Collectively, these data highlight the need for ongoing vigilance concerning the impact of azithromycin MDA on organisms other than those that are the immediate target, but also suggest that infrequent (annual) MDA of azithromycin is unlikely to substantially affect macrolide resistance rates in Gram-positive organisms[18].

Our study has several limitations. First, and consistent with other studies assessing the impact of MDA, it was not blinded. Second, the diagnosis of scabies and impetigo was made on clinical grounds alone, albeit by a single experienced physician using criteria which have previously been shown to have good sensitivity and specificity[27]. Thirdly, follow-up rates differed between our two study arms. In one village in the ivermectin-only treatment arm, rumours circulated that MDA was being conducted without approval from the local hospital even though hospital staff made up the majority of the field-team. Meetings were held with community leaders and the study team including the hospital Director of Nursing (RA), but follow-up in this village remained lower than other villages in the study. Despite this, we had an adequate sample size to demonstrate that there was no additional reduction in impetigo prevalence in the arm receiving combined treatment and our sensitivity analysis was consistent with our overall results. Fourth, we did not collect swabs from all individuals with active impetigo (nor from every lesion on individuals with multiple lesions). We cannot exclude the possibility that increasing the proportion of individuals from whom swabs were collected might have altered the proportion of samples containing pyogenic streptococci or macrolide-resistant bacteria. Finally, samples were shipped to Australia, a journey which might also have reduced our pathogen recovery rate. However, we successfully isolated *S. aureus*, a streptococcus or both from more than 95% of swabs so think it unlikely that the transport process affected our results. Our results are consistent with previous studies on changing patterns of carriage of antimicrobial resistant flora following MDA and provide some of the first bacteriological endpoint data on the impact of ivermectin MDA on impetigo.

Our data add to those from a small number of previous studies examining the potential of combining individual MDA programmes into a single intervention. Our study did not aim to investigate the safety of co-administration of ivermectin and azithromycin, as existing
pharmacokinetic and trial data already support the safety of co-administration of these agents[25,26] and we have recently completed a large scale field study directly addressing the question of safety at a district-level (ACTRN12613000474752). Although we were unable to detect any clinical impact on impetigo prevalence of adding azithromycin to ivermectin MDA on impetigo prevalence, co-administration still has potential logistical and financial benefits by treating multiple NTDs via a single intervention. Further studies on integrated approaches are needed to draw firmer conclusions about the potential benefit on disease occurrence.

Ivermectin MDA has emerged as a central component of the control strategy for scabies in high prevalence communities. Our data suggest the addition of a single dose of azithromycin, at a single timepoint, neither translates to an additional benefit in reducing impetigo prevalence at twelve months nor results in an increased prevalence of antimicrobial resistance. It is not known whether alternative strategies, such as biannual MDA or use of an alternative antimicrobial agent, might be more successful. Further investigation may help to optimise community interventions for the control of scabies and its sequelae.
Contributors:

MM wrote the first draft of the paper. CB, KA, EP conducted laboratory work. MM, HT, CK, JA, RA conducted fieldwork. MM, CB, KA, analysed the data. MM, JD, JKM, LR, MRM, DM, AWS, DCWM, AS designed and supervised the study. All authors revised the manuscript.

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Declaration of Interests:

JD reports grants from International Trachoma initiative. MM reports consultancy fees from the World Health Organisation. All other authors have no competing interests to declare.
References:


26. Amsden GW, Gregory TB, Michalak CA, Glue P, Knirsch CA. Pharmacokinetics of Azithromycin and the Combination of Ivermectin and Albendazole When Administered...


## TABLE 1: Demographics

<table>
<thead>
<tr>
<th></th>
<th>Ivermectin Only Arm</th>
<th>Combined Treatment Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>12 Months Follow-Up</td>
</tr>
<tr>
<td>Resident population</td>
<td>717</td>
<td>627</td>
</tr>
<tr>
<td>Enrolled population (%)</td>
<td>638 (88.9%)</td>
<td>478 (76.2%)</td>
</tr>
<tr>
<td>Gender (male) (%)</td>
<td>326 (51.1%)</td>
<td>212 (44.4%)</td>
</tr>
</tbody>
</table>
TABLE 2: Prevalence of Scabies and Impetigo

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>12 Months</th>
<th>Absolute Reduction</th>
<th>Relative Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ivermectin Only</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Scabies</strong></td>
<td>11.8%</td>
<td>1.0%</td>
<td>10.8%</td>
<td>91.5%</td>
</tr>
<tr>
<td></td>
<td>(95% CI 9.4 – 14.6%)</td>
<td>(95% CI 0.3 – 2.6%)</td>
<td>(95% CI 8.0 - 13.4%)</td>
<td>(95% CI 68.5 – 100%)</td>
</tr>
<tr>
<td></td>
<td>(n = 75/638)</td>
<td>(n = 5/478)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Impetigo</strong></td>
<td>10.1%</td>
<td>2.5%</td>
<td>7.6%</td>
<td>75.2%</td>
</tr>
<tr>
<td></td>
<td>(95% CI 8.1 – 13.0%)</td>
<td>(95% CI 1.4 -4.5%)</td>
<td>(95% CI 5.1 – 10.6%)</td>
<td>(95% CI 67.9 – 100%)</td>
</tr>
<tr>
<td></td>
<td>(n = 66/638)</td>
<td>(n = 12/478)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined Treatment</td>
<td>Scabies</td>
<td></td>
<td></td>
<td>Impetigo</td>
</tr>
<tr>
<td>--------------------</td>
<td>---------</td>
<td>-------</td>
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<td>---------</td>
</tr>
<tr>
<td></td>
<td>9.2%</td>
<td>0.7%</td>
<td>8.5%</td>
<td>92.4%</td>
</tr>
<tr>
<td></td>
<td>(95% CI 7.1 – 11.7%)</td>
<td>(95% CI 0.2 – 1.8%)</td>
<td>(95% CI 6.2 – 10.8%)</td>
<td>(95% CI 49.2 – 100%)</td>
</tr>
<tr>
<td></td>
<td>(n = 60/653)</td>
<td>(n = 4/605)</td>
<td>(n = 4/605)</td>
<td>(n = 4/605)</td>
</tr>
<tr>
<td></td>
<td>12.1% (95% CI 9.7% - 14.9)</td>
<td>3.3% (95% CI 2.1 – 5.1%)</td>
<td>8.8% (95% CI 5.9 – 11.7%)</td>
<td>72.7% (95% CI 48.9 – 96.5%)</td>
</tr>
<tr>
<td></td>
<td>(n = 79/653)</td>
<td>(n = 20/605)</td>
<td>(n = 20/605)</td>
<td>(n = 20/605)</td>
</tr>
</tbody>
</table>
**TABLE 3: Impetigo culture results**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>3 Months</th>
<th>12 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Organism isolated</strong> (%)</td>
<td><em>Organism isolated</em> (%)</td>
<td><em>Organism isolated</em> (%)</td>
<td><em>Organism isolated</em> (%)</td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ivermectin Only</strong></td>
<td><em>Staphylococcus aureus</em> 27/35</td>
<td>13/19</td>
<td>6/6</td>
</tr>
<tr>
<td></td>
<td>(77%, 59-89%)</td>
<td>(68%, 43-86%)</td>
<td>(100%, 52-100%)</td>
</tr>
<tr>
<td></td>
<td><em>Pyogenic streptococci</em> 28/35^</td>
<td>9/19^</td>
<td>1/6</td>
</tr>
<tr>
<td></td>
<td>(80%, 63-91%)</td>
<td>(47%, 25 – 71%)</td>
<td>(17%, 9-64%)</td>
</tr>
<tr>
<td><strong>Combined Treatment</strong></td>
<td><em>Staphylococcus aureus</em> 32/38</td>
<td>15/17</td>
<td>13/16</td>
</tr>
<tr>
<td></td>
<td>(84%, 68-93%)</td>
<td>(88%, 62 – 98%)</td>
<td>(81%,54-95%)</td>
</tr>
<tr>
<td></td>
<td><em>Pyogenic streptococci</em> 17/38^</td>
<td>5/17^</td>
<td>4/16</td>
</tr>
<tr>
<td></td>
<td>(45%, 29-63%)</td>
<td>(29%, 11 – 56%)</td>
<td>(25%, 8-53%)</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><em>Staphylococcus aureus</em> 59/73</td>
<td>28/36</td>
<td>19/22</td>
</tr>
</tbody>
</table>
Pyogenic streptococci* 45/73 (62%, 49-73%)

14/36 (39%, 24 – 56%)

5/22 (23%, 9-46%)

*For simplicity we report Group C/G Streptococci alongside S. pyogenes.

^One group C/G streptococcus in the ivermectin-only treatment arm and four in the combined treatment arm

#Two group C/G streptococcus in the ivermectin-only treatment arm.

TABLE 4: Antimicrobial sensitivity testing results

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>3 Month</th>
<th>12 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrolide Resistant</td>
<td>(%, 95% CI)</td>
<td>Macrolide Resistant</td>
<td>Macrolide Resistant</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(%, 95% CI)</td>
</tr>
<tr>
<td></td>
<td><em>Staphylococcus aureus</em></td>
<td>(%)</td>
<td>(95% CI)</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-------------------------</td>
<td>-----</td>
<td>---------------------</td>
</tr>
<tr>
<td><strong>Ivermectin Only</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>0/27</td>
<td>0/13</td>
<td>(0%, 0-16%)</td>
</tr>
<tr>
<td>*<em>Pyogenic streptococci</em></td>
<td>0/30</td>
<td>0/9</td>
<td>(0%, 0-14%)</td>
</tr>
<tr>
<td><strong>Combined Treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>1/32</td>
<td>8/15</td>
<td>(3%, 0-18%)</td>
</tr>
<tr>
<td>*<em>Pyogenic streptococci</em></td>
<td>0/19</td>
<td>0/5</td>
<td>(0%, 0-21%)</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>1/59</td>
<td>8/28</td>
<td>(1.7%, 0-10%)</td>
</tr>
<tr>
<td>*<em>Pyogenic streptococci</em></td>
<td>0/45</td>
<td>0/14</td>
<td>(0%, 0-13%)</td>
</tr>
</tbody>
</table>

*For simplicity we report Group C/G streptococci alongside S. pyogenes.*