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The Importance of Scabies Co-Infection in the Treatment Considerations for Impetigo

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Acknowledgements: We thank the participants and their families who contributed to this trial in
the hope of finding a better treatment option for their sores. We thank Irene O’Meara as the project manager for this trial and Linda Ward for her assistance in statistical analysis.
Abstract

Background: Skin infections account for a high disease burden in Indigenous children living in northern Australia. Although the relationship between impetigo and scabies is recognised, the prevalence of scabies in children with impetigo is not well reported. We report the prevalence, demographics and treatment success outcomes of impetigo and scabies co-infection in Indigenous children who were participants in a randomized controlled trial of impetigo treatment conducted in remote communities of the Northern Territory, Australia.

Methods: Of 1715 screening episodes for impetigo, 508 children were randomized to receive intramuscular benzathine benzylpenicillin (BPG), twice daily co-trimoxazole (SXT) for 3 days (4mg/kg trimethoprim plus 20mg/kg sulphamethoxazole per dose) or once daily co-trimoxazole (SXT) for 5 days (8mg/kg trimethoprim plus 40 mg/kg sulphamethoxazole per dose). A clinical diagnosis of scabies, tinea of the skin, scalp or nail, and head lice was made on all children. Scabies presence was not confirmed using diagnostic scrapings. In a post-hoc analysis, we determined whether co-infection with scabies had an impact on treatment success for impetigo.

Findings: Of children randomized to receive treatment for impetigo, 84/508 (16.5%) had scabies. The presence of scabies ranged from 14.3% to 20.0% in the three treatment groups. Treatment success for impetigo with and without scabies co-infection, independent of the treatment groups, was 75.9% and 86.6% respectively, absolute difference 10.7% (95% CI +1% to +21%). Treatment success for impetigo with and without scabies co-infection in the BPG group was 69.6% and 88.0% respectively, absolute difference 18.4% (95%CI –1 to +38%). In the pooled SXT groups the treatment success for impetigo with and without scabies co-infection was 78.6% and 86.0% with absolute difference 7.4% (95%CI –4 to +18%). Treatment success in
the pooled SXT group with scabies (78.6%) was higher than in the BPG group (69.6%) with scabies, absolute difference 9.0% (95% CI +0.1 to +18%). Prediction of treatment success for impetigo is dependent on the presence or absence of scabies and for scabies co-infected impetigo it was higher in the group treated with SXT.

Conclusions: The burden of scabies in an impetigo trial for Indigenous children was high. Treatment success for scabies co-infection was lower than for impetigo overall, with a higher success seen in the co-trimoxazole group than the benzylpenicillin group.
Introduction

Impetigo and scabies are the most common skin infections affecting Indigenous children and are endemic in the Top End of Australia. The prevalence of impetigo and scabies in children living in remote Australian Indigenous communities is very high and up to 10 – 70% at any one time\textsuperscript{1-4} with the highest rates found in those living in the most disadvantaged settings\textsuperscript{5}. The worldwide prevalence of scabies\textsuperscript{4} and global epidemiology of impetigo\textsuperscript{3} have recently been reported from systematic reviews. These reviews found that scabies and impetigo are common problems in childhood in developing countries and in marginalized communities in high-income countries\textsuperscript{3,4} and are closely correlated\textsuperscript{3}. Both studies found the highest burden in children from the Pacific region\textsuperscript{3,4}.

Scabies lesions are itchy and frequent scratching often results in secondary infection with bacterial pathogens\textsuperscript{6,7}. \textit{Streptococcus pyogenes} is usually the primary pathogen in secondarily infected scabies\textsuperscript{8}, while \textit{Staphylococcus aureus} is often considered a co-colonizer. Streptococci and staphylococci have previously been isolated from mite faecal pellets resulting in the hypothesis that the mite itself can also contribute to the spread of the pathogenic bacteria\textsuperscript{9}. In addition, scabies mites have recently been found to secrete proteins that have human complement inhibitory activity and these proteins have been reported to promote bacterial growth \textit{in vitro}\textsuperscript{10,11}. Poor hygiene has also been postulated as an important risk factor in the development of streptococcal skin sepsis following scabies\textsuperscript{12}. Where tropical climates prevail, children with scabies are two to seventimes more likely to have impetigo than children without scabies\textsuperscript{13}.

Untreated scabies infestations may become secondarily infected, and result in serious invasive bacterial infections\textsuperscript{2,14,15}. In addition, once scabies lesions become infected with \textit{S. pyogenes}, the host is at risk of the immunological consequences of \textit{S. pyogenes} infection.
including post-streptococcal glomerulonephritis and probably, acute rheumatic fever (ARF). The burden of ARF and rheumatic heart disease (RHD) in the Indigenous population of Australia is amongst the highest reported in the world and streptococcal skin infections, driven at least in part by antecedent scabies, are considered a major contributor to this burden, even though the skin-throat-S. pyogenes-ARF immunopathogenetic pathways remain to be fully elucidated.

We describe the burden of scabies interacting with impetigo and treatment success from a randomized controlled trial (RCT) of the treatment of impetigo. Specifically, we:

a) Describe the prevalence of scabies in Indigenous children who were screened for participation in the Skin Sore Trial;

b) Describe the demographics of those children randomized in the trial;

c) Assess the impact that scabies presence had on treatment success in the Skin Sore Trial;

and

d) Assess for seasonal variation in the presence of impetigo and scabies.

Materials and Methods

Setting and Population

Indigenous children from seven remote communities in the Northern Territory were screened for participation in the Skin Sore Trial, described elsewhere. Briefly, this large RCT compared two short courses of an oral antibiotic co-trimoxazole (SXT), against intramuscular injection of benzathine benzylpenicillin (BPG), the standard treatment for skin sores in our region. Intramuscular injection of benzathine penicillin is painful, which might deter parents and health-care providers from providing this treatment to children. In addition, treatment adherence is higher with shorter duration of oral treatments. There were 1715 children screened.
by research nurses for skin sores at either the school, local health center, or at home and details recorded on the case report form (CRF). Participation in the Skin Sore Trial was permitted every 90 days, as skin sores recur and many children present for treatment of sores several times a year. It was also postulated that the treatment effects of the regimens trialed would have no ongoing efficacy after the brief intervention (for oral antibiotics) and up to a maximum of one month (for intramuscular antibiotics). Of the screened participants, 508 children were randomized to participate over 663 enrolments. All analysis has been restricted to the child’s first participation in the trial. This is a post-hoc analysis of the Skin Sore Trial with the focus on scabies. Recruitment took place in communities from the Top End and Central Australia. The Top End has a tropical climate divided into two dominant seasons, a wet season (November through April with maximal precipitation and high humidity) and a dry season (May through October with high daily temperatures, lower overnight temperatures and reduced humidity). Central Australia has a temperate, arid climate. Numbers were small from Central Australia, which precluded an analysis of the variation by season in this region.

Participants were randomized 1:1:1 to receive a single dose of intramuscular BPG or one of two short courses of oral SXT. These courses were either three days of twice daily SXT (4+20mg/kg/dose) or five days of once daily SXT (8+40mg/kg/dose). Trial participants were seen at baseline, day 2 and day 7 for skin sore swabs and photographs of the one (mild) or two sores (severe) under investigation. Severity was stratified into mild impetigo, defined as one purulent or crusted sore and fewer than 5 sores in total or severe impetigo defined as >5 total body sores or ≥2 crusted or purulent sores. Treatment success was defined as any sore that was deemed to have improved or healed by day 7 when paired digital images of the sores were
viewed by expert assessors, blinded to treatment allocation\textsuperscript{7,20}. In participants with two assessed sores in the severe group, both were required to have been successfully treated.

**Scabies assessments**

At the initial screening visit, research nurses recorded the presence of impetigo, scabies, tinea of the skin, scalp or nail and headlice. In the subsequent enrolment visit, study staff recorded the presence of scabies, impetigo and whether the lesions were purulent or crusted. Research nurses were trained to screen and identify impetigo and scabies with a manual developed in previous work by the group\textsuperscript{7,21}. This training was overseen by the study doctor. Scabies presence was not confirmed using diagnostic scrapings. Children with clinically detected scabies (e.g. pustules and impetigo that were associated with severe itch or presence of burrows) were provided with a scabicide cream (5\% permethrin, Lyclear\textsuperscript{®}) and verbal advice given on the appropriate use of the cream. While antibiotic treatment of impetigo was directly observed, there was no confirmation that the scabicide was applied.

**Ethics statement**

The Skin Sore Trial is registered (Australian and New Zealand Clinical Trials Registry N12609000858291) and was approved by the Human Research Ethics Committee of the Northern Territory Department of Health and Menzies School of Health Research (09/08). Written informed consent was obtained from the parent or guardian of all participants.
Statistical analysis

Data were analyzed using STATA13 (Statacorp, College Station, TX). For categorical data, statistical significance was tested using Pearson’s chi2. For non-parametric data, statistical significance was tested using the Mann-Whitney test with p<0.05 being considered significant.

Results

Over the 3-year study period, there were a total of 1715 screening episodes for inclusion. Data on the clinical detection of scabies was available for 1665/1715 (97.0%) screened children. Children with scabies were twice as likely to have impetigo that needed to be treated OR 1.9 (95% CI 1.4 –2.6), P<0.0001) than children without scabies (Table 1). Of those screened, 508 children (median age 7.0 years, 48.0 % females) were randomized into three treatment groups: 165 children to BPG, 175 children to twice daily SXT for 3 days (SXT 3) and 168 children to once daily SXT for 5 days (SXT 5). Two children randomized to the BPG group withdrew from the study before further data was collected. Baseline characteristics divided by the presence and absence of scabies are shown in Table 2. Scabies was diagnosed clinically in 84/508 (16.5%) participants. The presence of scabies ranged from 14.3% to 20.0% in the three treatment groups (Figure 1). Scabies was diagnosed in 35/184 (19.0%) children aged ≤5 years, 33/222 children (14.9%) aged 6–9 years and 16/100 children (16.0%) aged 10–13 years (no difference in scabies prevalence by age group, p=0.53; Table 3). Children with scabies were more likely to have severe impetigo (88.1%) compared to those without scabies (68.5%) (p<0.01). Children with scabies were more likely to have upper limb impetigo than those without scabies (38.4% vs 26.5%, p <0.01) and less likely to have lower limb impetigo (38.4% vs 57.5%, p <0.001).
Treatment success for impetigo with and without scabies co-infection, independent of the
treatment groups was 75.9% and 86.6% respectively, absolute difference 10.7% (95% CI +1% to
+21%, Table 4). Treatment success for impetigo with and without scabies co-infection in the
BPG group was 69.6% and 88.0% respectively, absolute difference 18.4% (95%CI –1% to 38%).
In the pooled SXT group the treatment success of impetigo with and without scabies co-infection
was 78.6% and 86.0% with absolute difference 7.4% (95%CI –4% to +18%). Prediction of
treatment success was dependent on the presence or absence of scabies (Table 4). Our previous
study found no increased association between MRSA and scabies detection.

Most children (463/508; 91.0%) were located in the tropical region, known as the Top
End with (45/508; 9.0%) living in Central Australia, a desert climate. Scabies prevalence was
17.8% in the Top End and 16.5% in Central Australia, p=0.47.

The proportion of children from the Top End with scabies co-infection enrolled in the
trial was not related to the season. There was no difference in the proportion with scabies in the
dry versus the wet season (p=0.47).

Discussion

In this study we have documented the impact that scabies has on the severity of impetigo
and the differential efficacy of impetigo treatment when scabies co-infection occurs. Our key
findings are that there is a high burden of scabies in Australian Indigenous children who were
screened and recruited into an impetigo trial, children with secondarily infected scabies tended to
have more severe impetigo, are possibly less likely to respond to treatment with antibiotics than
those without scabies, and that in the presence of scabies, treatment success may be more likely
to be achieved when oral SXT is used rather than BPG.
Almost 17.0% of children recruited into the trial had secondarily infected scabies. This is similar to the reported prevalence of scabies in the region and confirms the ongoing large disease burden of scabies and impetigo in Indigenous Australian children. Children who had scabies were more likely to have severe impetigo, which highlights the importance of addressing both the parasitic infestation and bacterial infection simultaneously. Although the prevalence of scabies in our study is high, it is similar to a national survey recently conducted in Fiji, which reported scabies prevalence of 18.5%. In their study, scabies was very strongly associated with impetigo contributing to 93.0% of the risk.

We have reported a significantly lower treatment success for participants with scabies infected impetigo than those without. In those without scabies, treatment success was achieved in 87.0%, which was similar to the overall treatment success for the impetigo trial of 85.0%. This suggests that the absence of scabies was associated with treatment success. While this may in part relate to the generally greater severity of impetigo in those with scabies, the potential adverse impact of scabies on local host innate immune responses to bacterial skin infection also needs consideration and further evaluation. In addition, there is a difference in treatment success between those treated with BPG and those treated with either of the two short courses of oral SXT. This post-hoc analysis warrants further investigation of the possible reasons for this. Early case reports did not confirm efficacy of SXT for the treatment of scabies. Despite this, SXT has activity against other parasites e.g. pediculosis and further animal and human studies are needed to tease out this observation and whether SXT may have “mite killing” activity. It is unlikely that this difference in treatment success is driven by the presence of methicillin resistant S. aureus (MRSA) in children with scabies, as there was no increased association between MRSA and scabies detection observed in logistic regression models. The only microbiological
association with the presence of scabies in the trial was an increased chance of detecting *S. pyogenes* (OR 2.2, 95% CI 1.1% – 4.4%)\(^{20}\). Microbiology alone, cannot explain this difference in treatment success.

We found no difference in scabies prevalence by age group. This finding differs from a previous study in the same region that reported scabies to be more prevalent in children less than one year old\(^{27}\), but is similar to the high scabies burden throughout childhood reported from Africa, South America and Fiji\(^{23,28,29}\). In an impoverished community in rural Brazil, it was reported that the highest prevalence of scabies was in children four years or younger\(^{28}\). In a study performed in Sierra Leone, the reported prevalence of scabies was as high as 77.0% in the under five year olds and up to 86.0% in the 5–9 year olds\(^{29}\). In Fiji, it was reported that the prevalence of scabies was the highest in children between the ages of five to nine years\(^{23}\). We have been unable to detect a difference in the rate of scabies by age group in this trial, although the majority of participants were aged between five and nine years, which is the peak period of impetigo occurrence\(^{14}\). The other possible reason why there was no difference in scabies prevalence by age group is that all the children recruited into the trial had impetigo, which in itself pre-selects for higher scabies prevalence.

Mite movements are temperature-dependent, with increased transmission of mites in a warm environment\(^{30}\). Nevertheless a study in Malawi, which looked at the prevalence and seasonal associations of scabies and impetigo, found that scabies was more prevalent during the cold, dry season, most likely secondary to close interpersonal contact in crowded indoor environments. In contrast, there was an increase in the prevalence of impetigo during the wet season, which was attributed to poor hygiene\(^{31}\). In our study, we did not show a seasonal difference in impetigo or scabies.
The prevalence of scabies was 16.5% in this study, with inter-community variation. The range in prevalence was between 4.4% and 25.0%, with the highest rates found in two of the larger communities in the Northern Territory where overcrowding is especially common, with a median number of people per bedroom ranging between two and eight\textsuperscript{32, 33}. This variation in scabies prevalence between communities is important to note, as it identifies communities where interventions may be of a higher priority.

Our study had several limitations. This is a post-hoc analysis of a randomized controlled, non-inferiority trial comparing two treatments for impetigo. While the presence of scabies mites was not confirmed using scrapings and microscopy, a clinical diagnosis remains the standard of care and our study used visual aids to train staff in making this diagnosis\textsuperscript{20}. Although scabies treatment was recommended for all children with scabies and permethrin provided, treatment was not directly observed. Randomization was not stratified by the presence of scabies. Despite this, the baseline characteristics of those with and without scabies were similar. Strengths of our study include the randomized controlled trial design with equal distribution of characteristics between treatment groups, a high prevalence of scabies which make our findings robust, and the consistent reporting of skin infections by research nurses trained in clinical assessments using a published manual with written and visual descriptions of sores and scabies\textsuperscript{21}. 

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Acknowledgements

We thank the participants and their families who contributed to this trial in the hope of finding a better treatment option for their sores. We thank Irene O’Meara as the project manager for this trial and Linda Ward for her assistance in statistical analysis.
References


Figure 1: Flow chart of trial participants including the presence of scabies
Table 1. The presence and absence of scabies in participants screened for randomisation.

<table>
<thead>
<tr>
<th></th>
<th>Scabies positive</th>
<th>Scabies negative</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Sore requiring treatment *</td>
<td>154</td>
<td>64%</td>
<td>684</td>
</tr>
<tr>
<td>Flat/dry or no sores</td>
<td>87</td>
<td>36%</td>
<td>740</td>
</tr>
<tr>
<td>Total</td>
<td>241</td>
<td></td>
<td>1424</td>
</tr>
</tbody>
</table>

* Purulent or crusted sore

**Data on clinical detection of scabies was available for 1665/1715 screened children
Table 2. Distribution of study characteristics of trial participants based on presence or absence of scabies.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Scabies positive</th>
<th>Scabies negative</th>
<th>Total Study Cohort</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Female</strong></td>
<td>44/84 (52.4%)</td>
<td>200/424 (47.2%)</td>
<td>244/508 (48.0%)</td>
<td>0.36</td>
</tr>
<tr>
<td><strong>Median Age (y)</strong></td>
<td>6.9 (5.7-8.1)</td>
<td>7.1 (6.9-7.5)</td>
<td>7.1</td>
<td>0.5</td>
</tr>
<tr>
<td><strong>Severe Impetigo</strong></td>
<td>74/84 (88.1%)</td>
<td>290/422** (68.7%)</td>
<td>364/506 (71.9%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Weight in kg (median)</strong></td>
<td>20.8</td>
<td>20.6</td>
<td>20.4</td>
<td>0.5</td>
</tr>
<tr>
<td><strong>Height in cm (median)</strong></td>
<td>123</td>
<td>121</td>
<td>122</td>
<td>0.86</td>
</tr>
<tr>
<td><strong>Household where other children also had sores (%)</strong></td>
<td>44/84 (52.4%)</td>
<td>198/422** (46.9%)</td>
<td>242/506 (47.8%)</td>
<td>0.376</td>
</tr>
<tr>
<td><strong>Location of sores</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Upper limbs</strong></td>
<td>63/159 (38.4%)</td>
<td>162/612 (26.5%)</td>
<td>213/771 (27.6%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Lower limbs</strong></td>
<td>61/159 (38.4%)</td>
<td>352/612 (57.5%)</td>
<td>555/771 (72%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other</td>
<td>35/159</td>
<td>98/612</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------</td>
<td>---------</td>
<td>---------</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(22.0%)</td>
<td>(16.0%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Denominator larger because some children had more than one sore enrolled in the study.

** 2 children randomized in the study withdrew before any data was collected
Table 3. Scabies distribution by age group in children enrolled in the trial.

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Scabies positive n=84</th>
<th>Scabies negative n=422</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>3m–5y (n=184)</td>
<td>35</td>
<td>19.0</td>
<td>149</td>
</tr>
<tr>
<td>6y–9y (n=222)</td>
<td>33</td>
<td>14.9</td>
<td>189</td>
</tr>
<tr>
<td>10y–13y (n=100)</td>
<td>16</td>
<td>16.0</td>
<td>84</td>
</tr>
</tbody>
</table>
Table 4. Intention to treat outcome.

<table>
<thead>
<tr>
<th>Treatment Success</th>
<th>Scabies positive (Point Estimate)</th>
<th>95% CI</th>
<th>Scabies negative (Point Estimate)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPG (n=165)</td>
<td>69.6%</td>
<td>49.2%-89.9%</td>
<td>88.0%</td>
<td>82.3%-93.6%</td>
</tr>
<tr>
<td>SXT 3 (n=175)</td>
<td>81.8%</td>
<td>64.3%-99.3%</td>
<td>84.9%</td>
<td>78.9%-90.9%</td>
</tr>
<tr>
<td>SXT 5 (n=168)</td>
<td>76.5%</td>
<td>61.4%-91.4%</td>
<td>87.1%</td>
<td>81.4%-92.7%</td>
</tr>
<tr>
<td>Pooled SXT (n=343)</td>
<td>78.6%</td>
<td>67.5%-89.7%</td>
<td>86.0%</td>
<td>81.9%-90.1%</td>
</tr>
<tr>
<td>All patients (n=508)</td>
<td>75.9%</td>
<td>65.0%-84.9%</td>
<td>86.6%</td>
<td>82.9%-89.8%</td>
</tr>
</tbody>
</table>
Figure 1.

1715 screened for eligibility
241 (14.1%) scabies positive
1424 (83.0%) scabies negative
50 (2.9%) scabies unknown

1052 excluded
345 did not meet inclusion criteria
253 flat or dry sores only
16 outside age range
21 oral anthelminths within 7 days
35 benzathine benzydamycin within 30 days
2 abscess
11 boils
11 unavailable for 7 days follow-up
21 declined to participate
106 eligible but not able to be located at time of potential recruitment

663 eligible for randomisation
202 mild
461 severe

155 randomly allocated at second visit or later

508 randomly allocated at first visit
84 (16.5%) scabies positive
424 (83.5%) scabies negative

165 participants allocated
benzathine benzydamycin
25 (15.3%) scabies positive
140 (84.7%) scabies negative

343 participants allocated co-
trimoxazole

175 allocated to co-trimoxazole for 3 days
35 (20.3%) scabies positive
140 (80.0%) scabies negative

168 allocated to co-trimoxazole for 5 days
24 (14.3%) scabies positive
144 (85.7%) scabies negative