Prevalence, Clinical Features, and Antibiotic Susceptibility of Group A Streptococcal Skin Infections in Schoolchildren in Urban Western and Northern Uganda

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Abstract

Background: Group A Streptococcus (GAS) skin infections can lead to invasive sepsis, post-streptococcal glomerulonephritis, and potentially rheumatic heart disease (RHD). Within a study to identify predisposing factors of RHD in Ugandan schoolchildren, we determined the prevalence of skin infections and assessed the clinical features and antibiotic susceptibility of GAS skin infection.

Methods: Cross-sectional study conducted at 3 urban primary schools in Western and Northern Uganda in March 2017. A dermatologist rendered clinical diagnoses and obtained a skin swab specimen from lesions with signs of bacterial infection. Beta-hemolytic colonies underwent Lancefield grouping, species identification by polymerase chain reaction, and antimicrobial susceptibility testing.

Results: From 3265 schoolchildren, we observed 32% with ≥1 fungal, 1.8% with ≥1 bacterial, 0.9% with ≥1 viral, and 0.2% with ≥1 ectoparasitic infection. 32% (25 of 79) of specimens were GAS-positive, of which one-third demonstrated tetracycline resistance. Of 17 impetigo cases,

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13 (76%) were located on the leg/foot and 3 (18%) on the head/neck. Prevalence of GAS skin infection was 0.8% (25 of 3265). In Northern Uganda, where subclinical definite RHD prevalence is 1.1%, GAS skin infection prevalence was 1.2% (4 of 343) and 0.9% (3 of 352).

Conclusion: This study identifies tetracycline-resistant GAS in Ugandan communities, suggests modified skin examination of exposed anatomic locations may be appropriate for population-based GAS skin infection studies, and underscores need for clear case definitions of GAS skin infection. Future studies are needed to evaluate the role of GAS skin infection in development of RHD in Ugandan communities.

Keywords

Group A Streptococcus; Streptococcus pyogenes; skin infection; children; Africa; Uganda

Background

Impetigo is the most common skin infection in children worldwide.(1) Globally, the population of children with impetigo at any one time is estimated to be at least 162 million, predominantly in tropical, resource-limited settings.(2) In low- and middle-income countries, the Lancefield group A β-hemolytic streptococcus (GAS, *Streptococcus pyogenes*) is the primary etiologic agent for impetigo(3), though *Staphylococcus aureus* can also cause the condition. Impetigo from GAS and *S. aureus* can causes complicated local skin infections, such as cellulitis and abscesses, as well as invasive infections that can be fatal. Additionally, it has been hypothesized that GAS skin infection could be linked to the pathophysiology of acute rheumatic fever and rheumatic heart disease (RHD) in impetigo-endemic settings.(4, 5) While RHD is endemic in Africa, there is little high-quality disease surveillance data on GAS.

Within the structure of a larger GAS study aimed at understanding drivers of RHD in Ugandan schoolchildren, we recognized an opportunity to address gaps in knowledge related to skin infections, including those of GAS etiology. In this cross-sectional study, we aimed to determine the prevalence of skin infections in urban Ugandan schoolchildren and assess the clinical features and antibiotic susceptibility of GAS skin infection in this population.

Methods

Study Setting

This cross-sectional study was conducted during the first week of March 2017 at 3 public primary schools in urban locations: 1 in Western Uganda (Mbarara) and 2 in Northern Uganda (Gulu). These schools were chosen because they were existing sites for enrollment in the National RHD Registry.(6) Additionally, the pediatric RHD prevalence was well characterized in Gulu (7), and small-scale epidemiological surveillance (unpublished) had also been conducted in Mbarara. Primary school enrollment, as a percentage of primary school-age children, is estimated to be 91% in Uganda.(8) Mbarara and Gulu have a tropical climate with year-round average high temperatures of 25.8C and 28.3C, respectively. Mbarara has four seasons that alternate between rainy and dry. In March, Mbarara is in

the middle of its first rainy season. Gulu has a long rainy season that runs from March to November and a shorter dry season from December to February.

Skin Examination & Clinical Diagnosis

By school class, participants were separated by gender, brought to a waiting area by their teacher, and examined in a private setting. Skin examination occurred in two-phases: 1) Phase 1: Full body skin screening examination by a local healthcare professional (nurse, clinical officer, or pediatrician) who had received training on identification of abnormal skin findings, including clinical signs of skin infection (bacterial, fungal, viral) and ectoparasitic infestation. Examination of the groin/buttocks and female breasts was deferred. 2) Phase 2: Positive phase one participants were evaluated by a board-certified dermatologist (A.Y.C), who rendered a clinical diagnosis. Clinical signs of bacterial infection were defined as pus, pustule, crust, or erythema. A distinction was made in clinical diagnosis between folliculitis of the scalp versus non-scalp as asymptomatic scalp carriage of GAS has been reported.[9]

Case Definition

GAS skin infection was defined as identification of GAS by polymerase chain reaction (PCR) assay from a skin specimen collected from a lesion with clinical signs of bacterial infection, as defined above.

Laboratory Methods

Skin Swab Collection—If crust, pus, or pustules were present, a skin surface swab was obtained from a single representative lesion—regardless of the clinical diagnosis. Of note, tinea capitis commonly presents with pustules and crust. Skin swabs were obtained in accordance with the study protocol. Fungal culture and potassium hydroxide staining were not performed. Similarly, folliculitis lesions were swabbed, though folliculitis can be caused by non-infectious and infectious etiologies (bacteria, virus, fungal, ectoparasite) with bacterial cultures often resulting as normal skin flora/culture-negative.[10] Each skin specimen was obtained using a flocked swab and placed in an individual transport vial containing skim milk, tryptone, glucose, glycerin broth (STGGB).[11]

Sample Transport to Central Laboratory—Skin swabs for culture were transported in a STGGB media placed in a sealed bag and inside a cold box with icepacks, as described previously.[11] These prepared samples were then frozen at −20C and transported to a central laboratory (MBN Clinical Laboratories) in Kampala, Uganda for plating. Samples were stored at −80C if not plated immediately upon arrival.

Skin Swab Culture and Streptococcal Grouping—The media and swab were fully thawed and then vigorously vortexed for about a minute. Fifty-microliters were then transferred onto 5% sheep blood agar, spread with a 10-uL plastic loop, and incubated at 35°C in 5% CO_2 for up to 48 hours. Plates were checked for beta-hemolytic colonies. These colonies were sub-cultured onto sheep blood agar until pure colonies were isolated. Pure beta-hemolytic colonies underwent Lancefield grouping into groups A,B,C,D,F or G based on the Oxoid Streptococcal grouping Kit (Code TSMX3981E, Oxoid, Cambridge, UK) following the manufacturer's instructions. Furthermore, all the beta-haemolytic streptococci

were also species identified by PCR for detection of any of Groups A, B, or C using the GenoType BC Gram Positive test (Hain Lifescience Nehren, Germany). About 10 pure colonies were emulsified in PCR water and DNA was extracted from the colonies using boiling method. Multiplex PCR was then performed on the GT thermocycler followed by nucleic acid reverse hybridization of amplicons on to species-specific probes fixed on a nitrocellulose membrane. PCR analysis for *Staphylococcus aureus* was outside the scope of this study.

Antibiotic Susceptibility Testing—Antibiotic susceptibility testing was performed on PCR-confirmed GAS bacterial isolates. Purified GAS colonies were selected for antimicrobial susceptibility testing (AST). The AST panel included ceftriaxone, penicillin, erythromycin, vancomycin, chloramphenicol, tetracycline, and ofloxacin. The standard disc diffusion method was used to test susceptibility of the GAS to the antimicrobials. A 0.5 McFarland bacterial suspension was prepared and inoculated on sheep blood Mueller-Hinton (MH) agar plates and incubated in 5% CO_2 for 24 hours at 37°C. Zone diameters were read and interpreted following the criteria of the Clinical Laboratory Standards Institute.(12)

Data Collection & Analysis

Clinical data were captured on paper, entered into an electronic REDCap® database, and analyzed with Stata/SE 15.0 (College Station, Texas, US). We organized the reporting of skin conditions using an approach similar to recent publications of school-based skin survey data.(13, 14) Utilizing the clinical diagnoses rendered in Phase Two, we report the number of different types of infectious skin conditions diagnosed and the point prevalence with 95% confidence interval (CI) in the population. Pearson's chi-squared tests were used to compare differences in prevalence by gender (male, female), age group (4–8 years, 9–12 years, 13–16 years, 17–20 years), study site, and region (Northern vs. Western Uganda). Differences were considered significant at a *p*-value of <0.05.

Ethics & Regulatory Approval

Institutional review board approval was obtained from Makerere University School of Medicine Research and Ethics Committee (final approval given by Uganda National Council for Science and Technology), Case Western Reserve University, and the University of California, San Francisco. An informational letter was sent home with all students informing parents of the study, and informational sessions were held for parents to obtain more information. Following this, an informed consent/assent form was sent home with all children, and only those returning these forms, and providing their assent (>8 years) were enrolled in the study.

Afebrile participants with skin bacterial infection received topical antibiotics and were re-evaluated in 2 days by the study nurse and changed to oral antibiotics for 7 days if not improved; febrile participants with skin bacterial infection were treated with oral antibiotics for 7 days and re-evaluated by the study nurse. Participants diagnosed with fungal infection received topical antifungals with the exception of tinea capitis for which griseofulvin was given with instruction to follow-up at the local health center. Benzyl benzoate was given for scabies infestation. Follow-up at the local health center was advised

for the remainder of conditions diagnosed. There was no cost to the student or family for evaluation, microbiology testing, or treatment that was provided by the study. Participants were sent home with a note alerting the family of an identified infection and the treatment plan, as well as contact information for the study nurse.

Results

Absenteeism was low, with greater than 95% attendance on the day of skin screening at each school. All children attending school on the days of skin screening participated in the study, resulting in a total of 3265 participants across 3 schools with 343 in Northern Uganda A, 352 in Northern Uganda B, and 2570 in Western Uganda. 51% of the 3265 participants (1677) were female. There was a difference in age for the 3 schools (p<0.05) and by region (p<0.05), with teenagers representing a larger proportion of participants at both Northern Ugandan primary schools. (See Table 1 for study participant demographics). Based on clinical diagnosis in all 3265 participants, we observed a prevalence of 32% (1050) for children with ≥1 fungal skin infection, 1.8% (60) for children with ≥1 bacterial skin infection, 0.9% (30) for children with ≥1 viral skin infection, and 0.2% (7) for children with ≥1 ectoparasitic infestation. Tinea capitis was the most common infectious skin condition, affecting just under one-third of the study population with a prevalence of 28% (934). See Table 2 for point prevalence with 95% CI of all infectious skin conditions.

Of the 1344 participants who screened positive for an abnormal skin finding in Phase 1, 87 were determined to have clinical signs of bacterial infection (crust, pus, pustule as defined in study protocol) and had a skin swab specimen collected for microbiology analysis. Of these 87 specimens, 79 had PCR results available. 25 of 79 specimens (32%) were positive for GAS by PCR. By site, the prevalence of GAS skin infection, as determined by PCR, was Northern Uganda A: 1.2% (4 of 343), Northern Uganda B: 0.9% (3 of 352), Western Uganda: 0.7% (18 of 2570). The overall study prevalence was 0.8% (25 of 3265).

For the 79 specimens analyzed by PCR, the clinical diagnoses were as follows: tinea capitis with pustules/crust (39%), impetigo (22%), folliculitis/furunculosis, non-scalp (20%), scalp folliculitis (18%), scabies (1%). GAS PCR-positive skin specimens were more likely to be associated with a clinical diagnosis of impetigo (p<0.05). (See Table 3). Of the 17 impetigo cases, 13 (76%) were located on the lower extremity (leg or foot), 3 (18%) on the head/neck, and 1 at an unspecified site. No impetigo cases were associated with scabies or eczematous dermatitis; the study prevalence of each was low: scabies: 0.18% (6 of 3265) and eczematous dermatitis: 1.8% (57 of 3265). Of the 15 non-scalp folliculitis cases, 12 (80%) were located on the lower extremity, 4 (27%) on head/neck, 1 on the upper extremity (arm), 1 on the back, and 1 at an unspecified site. By definition, all tinea capitis and scalp folliculitis cases were located on the scalp.

Of the 25 specimens with GAS identified by PCR, 21 had cultures that grew GAS. For these 21 GAS+ culture specimens, AST was performed. Six of 21 (29%) specimens demonstrated resistance to tetracycline (inhibition zone 15–18mm). One specimen demonstrated intermediate susceptibility to tetracycline (inhibition zone 22mm). The remaining 14

specimens (66%) were pan-sensitive. See Figure 1 for summary of participants' skin evaluation and microbiology results.

Discussion

Herein, we report prevalence data on infectious skin conditions and characterize GAS skin infection in schoolchildren in urban Northern and Western Uganda. In our study, the overall prevalence of GAS skin infection was 0.8%, as defined by identification of GAS by PCR in specimens obtained from skin lesions with pus, pustules, or crust.

Our point prevalence of 1.8% for bacterial skin infection (as determined by clinical diagnosis) falls within the prevalence range of 1.3% to 12.7% reported from schoolchildren in rural, mixed rural/urban, and urban areas of East Africa.(13, 15–20) These studies utilized clinical diagnosis to determine the presence or absence of bacterial skin infection; microbiology data were not reported.

Our low prevalence of GAS skin infection may be a reflection of an urban population's better access to water, sanitation, and hygiene.(21) Impetigo is more common in rural areas(2), and GAS skin infection is influenced by hygiene factors.(22) Another consideration is the potential impact of the Onchocerciasis Control Program, which utilizes mass drug administration of ivermectin twice yearly to households in endemic areas. In other world regions, impetigo is driven by scabies and when scabies is treated, both scabies and impetigo rates decline.(23, 24) If a similar relationship exists in Northern Uganda where onchocerciasis is endemic, a recent round of ivermectin prophylaxis could have treated scabies and impetigo before our study was conducted. Furthermore, measurements of point prevalence do not account for seasonal weather patterns. In monsoonal climates, GAS is more common in dry seasons, compared with wet ones.(25) If the same is true in Uganda, then an assessment during the dry seasons might identify a higher prevalence of GAS skin infection.

In Northern Uganda, where the subclinical definite RHD prevalence is 1.1%(7), we found the point prevalence of GAS skin infection to be 1.2% at one school and 0.9% at the other. While the prevalence of GAS skin infection is not nearly as high as in the Pacific region, where the strongest linkage between GAS skin infection and RHD exists, these data suggest that skin infection could plausibly be contributing to RHD, by contributing to the overall GAS burden in African communities. Future work is needed to help elucidate this potential connection.

The observation that about one-third of GAS skin specimens were resistant to tetracycline is consistent with other studies demonstrating tetracycline-resistance in the majority of GAS isolates from referral healthcare settings in sub-Saharan Africa(26–29) and another school-based study in East Africa.(30) Clinicians should be aware of tetracycline-resistant GAS in Ugandan communities, particularly as doxycycline is a common treatment for bacterial skin infections in East Africa, given its dosing, general tolerability, and widespread availability.

We utilized a two-phase skin examination workflow that proved to be an efficient method for integrating dermatology expertise within a large study population, nearly identical

to an approach used in a larger study of 13,019 schoolchildren in Cote d'Ivoire.(14) For population-based studies in settings where dermatologists are not available or other human resource constraints exist, a modified skin examination of exposed areas (head & neck, lower & upper extremities) may be appropriate, given that we found the anatomic distribution of GAS skin infections to be primarily in exposed areas.

Differences in GAS PCR result based on clinical diagnosis are not surprising. Of specimens submitted for GAS PCR, 4 of 31 (13%) cases of tinea capitis with pustules/crust and 1 of 14 (7%) cases of scalp folliculitis were GAS PCR positive. This finding could represent asymptomatic scalp carriage of GAS(9) or true GAS skin infection. As mentioned earlier, tinea capitis with pustules/crust would not typically lead a dermatologist to perform a bacterial culture, and folliculitis is understood to have a variety of etiologies with negative bacterial cultures commonplace.

Our study's high prevalence of fungal skin infections, particularly tinea capitis, is consistent with data from other school-based prevalence studies of skin conditions in East Africa.(13, 15–20) Pityriasis versicolor was more prevalent in Northern Uganda (p<0.05), likely due to the adolescent age of primary school students which predisposes to the condition. Northern Uganda is a post-conflict region where the local population is still experiencing substantial economic hardship and thus children are often delayed in schooling. Interdigital toeweb infection, which includes dermatophyte and candidal fungal infections, tended to be more prevalent in Western Uganda (p=0.07) and may be related to the observation that many schoolchildren were wearing damp stockings and socks.

Beyond the aforementioned considerations with interpretation of point prevalence data, our study has additional limitations. Our study was not designed to draw conclusions regarding the clinical drivers of GAS skin infection in Uganda. Further work will be needed in this area. Second, *S. aureus* is an important causative agent of bacterial skin infection, particularly bacterial folliculitis and furunculosis, but pertinent studies were outside the scope of this study. Finally and perhaps most importantly, the lack of uniform definitions for bacterial skin infections and GAS skin infection was a major challenge for this study. The broadest definition of pyoderma we found was "any variant of superficial bacterial skin infection (e.g. impetigo, impetigo contagiosa, ecthyma, folliculitis, "impetigo of Bockhart", furuncle, carbuncle, tropical ulcer, etc.)."(3) However, some authors distinguish folliculitis from pyoderma, infected wounds from tropical ulcer from impetigo, tropical ulcer from pyoderma(19), and abscess from pyoderma.(15) "Skin sore" has become synonymous with impetigo in the literature, but this description also applies to the clinical presentation of ecthyma, as well as a myriad of skin conditions that present with disruption of the skin barrier, such as herpes simplex virus, deep fungal infections, atypical mycobacterial infections, and non-infectious ulcers. Even when microbiology data are available, our study highlights the clinical-pathological discrepancies that can arise. For example, were the GAS PCR-positive cases of tinea capitis and scalp folliculitis appropriate to include as GAS skin infections when they could represent asymptomatic carriage? Should the criteria for GAS skin infection include a stipulation that an alternative explanation for signs of bacterial infection be excluded? With the research momentum around impetigo and pyoderma as related to GAS, achieving consensus on the case definition of GAS skin infection and

which clinical diagnoses comprise superficial bacterial skin infections should be a priority to ensure consistent methodology in future studies and facilitate appropriate interpretation of data.

In conclusion, future studies are needed to evaluate the role of GAS skin infection in the development of RHD in Ugandan communities. This study contributes school-based community prevalence data on infectious skin diseases, identifies tetracycline-resistant GAS in Ugandan communities, suggests that modified skin examination of exposed anatomic locations may be appropriate for population-based GAS skin infection studies, and underscores the need for clear case definitions of GAS skin infection.

Acknowledgements:

Abbreviated

GAS   Skin Infections Ugandan Schoolchildren

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                    ┌─────────────────────────────────┐
                    │  Total children at 3 primary schools │
                    │            N = 3265             │
                    └─────────────────────────────────┘
                                     │
                    ┌─────────────────────────────────┐
                    │ Skin screening by health professionals │
                    │            N = 3265             │
                    └─────────────────────────────────┘
                                     │
                    ┌─────────────────────────────────┐
                    │   Evaluation by dermatologist    │
                    │            N = 1344             │
                    └─────────────────────────────────┘
                                     │
                    ┌─────────────────────────────────┐        ┌──────────────────┐
                    │   Skin swab specimen obtained    │───────▶│ Missing PCR results │
                    │             N = 87              │        │      N = 8       │
                    └─────────────────────────────────┘        └──────────────────┘
                                     │
                    ┌─────────────────────────────────┐
                    │ Skin swab specimens with PCR results │
                    │            N = 79               │
                    └─────────────────────────────────┘
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Positive GAS-PCR
N = 25

Negative GAS-PCR
N = 54

Culture data:
- 2 No Growth
- 2 *Staph aureus*
- 20 GAS
- 1 GAS & *Staph aureus*

Culture data:
- 49 No Growth
- 3 *Staph aureus*
- 2 coagulase-negative Staph
- 1 oropharyngeal flora

21 specimens with positive GAS culture had antibiotic susceptibility testing performed to ceftriaxone, chloramphenicol, erythromycin, ofloxacin, penicillin, tetracycline, and vancomycin:
- 6 tetracycline-resistant
- 1 intermediate susceptibility to tetracycline
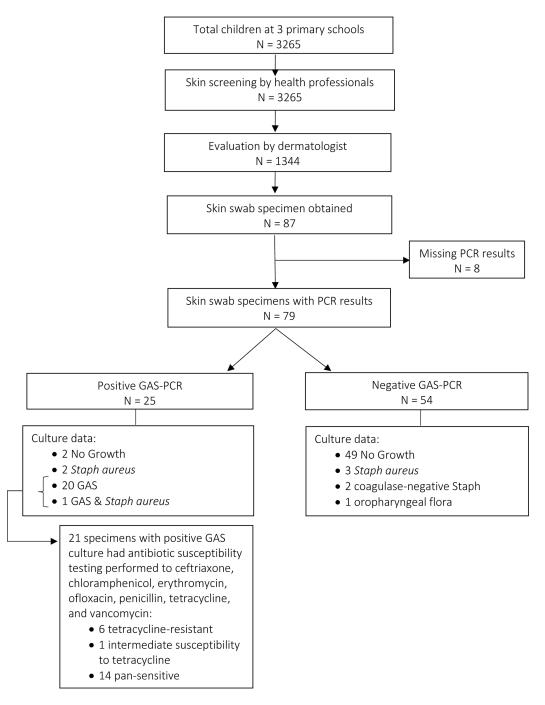- 14 pan-sensitive

Figure 1:
Flow chart of the school-based skin survey conducted at three primary schools in Northern Uganda (Gulu) and Western Uganda (Mbarara). PCR, polymerase chain reaction. GAS, Group A streptococcus.

Table 1:

Demographics of primary schoolchildren

Study Site	Northern Uganda A n=343	Northern Uganda B n=352	Western Uganda n=2570	Total n= 3265
Female	180 (53%)	162 (46%)	1335 (52%)	1677 (51%)
Age (years)				
4–8	52 (15%)	47 (13%)	894 (35%)	993 (30%)
9–12	149 (43%)	163 (46%)	1549 (60%)	1861 (57%)
13–16	140 (41%)	142 (40%)	125 (5%)	407 (13%)
17–20	2 (0.6%)	0	0	2 (0.06%)
Unknown	0	0	2 (0.08%)	2 (0.06%)

Table 2:

Point prevalence (95% confidence interval, CI) of skin infections based on clinical diagnosis

	Northern Uganda A		Northern Uganda B		Western Uganda		Total	
Children	343		352		2570		3265	
	N	*Prevalence (95% CI)*	*N*	*Prevalence (95% CI)*	*N*	*Prevalence (95% CI)*	*N*	*Prevalence (95% CI)*
Children with ≥1 fungal skin infection								
Total	114	33 (28–38)%	109	31 (26–36)%	827	32 (30–34)%	1050	32 (31–34)%
Tinea capitis	101	29 (25–34)%	70	20 (16–24)%	763	30 (28–31)%	934	28 (27–30)%
- with pustules/ crust	7	2.0 (0.5–3.5)%	4	1.1 (0.03–2.2)%	24	<1%	35	<1%
Tinea corporis	21	6.1 (3.6–8.7)%	24	6.8 (4.2–9.5)%	75	2.9 (2.2–3.6)%	120	3.7 (3.0–4.3)%
Tinea faciei	0	0	1	<1%	8	<1%	9	<1%
Tinea pedis	1	<1%	2	<1%	43	1.7 (1.2–2.2)%	46	1.4 (1.0–1.8)%
Tinea unguium	0	0	1	<1%	0	0	1	<1%
Interdigital toeweb	1	<1%	1	<1%	25	1.0 (0.6–1.4)%	27	<1%
Pityriasis versicolor	6	1.8 (0.4–0.3.1)%	24	6.8 (4.2–9.5)%	2	<1%	32	1.0 (0.6–1.3)%
Children with ≥1 bacterial skin infection								
Total	9	2.6 (0.9–4.3)%	6	1.7 (0.4–3)%	45	1.8 (1.2–2.3)%	60	1.8 (1.4–2.3)%
Impetigo	1	<1%	2	<1%	14	<1%	17	<1%
Folliculitis/ Furunculosis, non-scalp	4	1.2 (0.03–2.3%	2	<1%	17	<1%	23	<1%
Scalp folliculitis	3	<1%	2	<1%	10	<1%	15	<1%
Cellulitis	1	<1%	0	0	3	<1%	4	<1%
Pitted keratolysis	0	0	0	0	3	<1%	3	<1%
Children with ≥1 viral skin infection								
Total	0	0	1	<1%	29	1.1 (0.7–1.5)%	30	<1%
Verruca vulgaris	0	0	1	<1%	16	<1%	17	<1%
Molluscum contagiosum	0	0	0	0	10	<1%	10	<1%
Herpes simplex virus, oral labialis	0	0	0	0	3	<1%	4	<1%
Children with ≥1 ectoparasite infestation								
Total	0	0	1	<1%	6	<1%	7	<1%
Scabies	0	0	1	<1%	5	<1%	6	<1%
Tungiasis	0	0	0	0	1	<1%	1	<1%

Table 3.

Group A streptococcus (GAS) polymerase chain reaction (PCR) status by clinical diagnosis for 79 skin specimens

	Impetigo	Folliculitis/Furunculosis, non-scalp	Tinea capitis with pustules/crust	Scalp folliculitis	Scabies	
GAS PCR+	14 (82%)	6 (38%)	4 (13%)	1 (7%)	0	p<0.05
GAS PCR−	3 (18%)	10 (62%)	27 (87%)	13 (93%)	1	
Total, n=79	17	16	31	14	1	