Epidemiologic and Clinical Characteristics and Outcomes of Patients Diagnosed with Southern Tick Associated Rash Illness (STARI) – 2018-2019

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Title: Epidemiologic and Clinical Characteristics and Outcomes of Patients Diagnosed with Southern Tick Associated Rash Illness (STARI) – 2018-2019

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Running title: Characteristics and outcomes of STARI

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Abstract

In this study, we describe the clinical course and outcomes for 58 patients presenting with Southern tick-associated rash illness (STARI). Using 16S sequencing, no known bacterial pathogen was detected. Although an etiologic agent remains unknown, these results do provide updated information on rash color, shape, duration, and treatment outcomes.

Introduction:

Southern tick-associated rash illness (STARI) is a condition of unknown etiology that presents with a characteristic erythema migrans (EM) rash, sometimes described as a bullseye rash, and can also include symptoms of joint pain, fatigue, chills, or headache.[1] It mostly occurs in areas of the Southeast and South-Central United States and has been associated with the bite of the *Amblyomma americanum* (Lone Star) tick.[2] A previous report identifying *Borrelia lonestari* as the possible causative agent was not supported by subsequent investigations.[3] As such, no molecular or serological test is available for diagnosing STARI.[4] In the absence of a known etiologic agent or available diagnostic test, STARI diagnoses are based on symptoms, association with a tick bite, and location where the tick exposure likely occurred.[1]

Given the clinical similarities and route of transmission of STARI and Lyme disease, studies have been conducted to elucidate differences. [5,6] A publication from 2005 compared patients with EM rash from Missouri, where Lyme disease is rare, with patients from New York, where Lyme disease is endemic, and suggested that the Missouri patients were more likely to present with lesions smaller in size, more circular, and with more central clearing.[2,7] Missouri patients were also less likely to have other constitutional symptoms, less likely to have multiple rashes, and recovered more quickly than New York patients after antibiotic treatment.[2] However, since this study compared two patient populations with different illnesses and all patients received the same treatment, it cannot be determined whether antibiotics were beneficial for the patients diagnosed with STARI or if the clinical course improved more quickly regardless of treatment. In this report, we describe the demographic and clinical characteristics

of patients that present with signs and symptoms of STARI and how treatment with antibiotics affected persistence of rash or other symptoms.

Methods:

The Centers for Disease Control and Prevention's (CDC) Division of Vector-Borne Diseases, Bacterial Diseases Branch conducted a tick bite rash study from 2018 – 2019. Patient information was collected via two methods: enrollment through collaborating healthcare providers at the University of North Carolina (UNC) or through direct submission to CDC. For the direct submission process, patients found out about this study by word-of-mouth or through a devoted CDC website and chose to reach out and participate. In both instances, patients completed questionnaires about their rash and illness during two clinic visits (acute and convalescent phases of illness), and provided blood samples and tick specimens or pictures, when available.

To be eligible for this study, participants had to be at least three years of age, have an acute onset of an annular, erythematous, expanding EM-like rash at least 3 cm in diameter, a recent history of tick bite at the rash site or described potential exposure to ticks, no antibiotic treatment within the past month, and provide written informed consent or assent (for those under 14). The study protocol was reviewed and approved by Institutional Review Boards and ethics committees at the Centers for Disease Control and Prevention and the University of North Carolina - Chapel Hill.

Data were extracted from a REDCap database and analyzed using SAS® Studio. Chi-square and Fisher's exact tests were used to determine the comparability of the two study

groups and to summarize overall characteristics. Univariate analysis was conducted to evaluate the association between rash presence and duration by rash size at presentation, age, sex, use of non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics taken, time between visits, and other symptoms experienced. Logistic regression was used to determine the effects of antibiotic treatment on rash duration. All variables were tested at the alpha level 0.05. Blood samples taken at the two visits were tested using targeted V1-V2 16S rRNA metagenomic sequencing to identify potential bacterial pathogens as previously described.[8] In addition, serological testing was conducted on these samples at CDC using FDA-cleared, standard two-tier testing to rule out Lyme disease as the potential cause of illness. Cases with incomplete data from healthcare visits and those with any positive IgM or IgG Lyme serologic test results were excluded from analysis of antibiotic use and rash duration and other symptoms.

Results:

Patient Characteristics

The two groups differed significantly with respect to age, presence of comorbidities, and irregular boundary of rash (Table 1 and Table 2). Given the small sample sizes, individuals from the North Carolina cohort (n=11) and the CDC direct submission cohort (n=47) were combined for the analyses of patient characteristics at acute visit (n=58). The CDC direct submission cohort included patients reporting confirmed or potential tick exposure in Alabama, Arkansas, Florida, Georgia, Illinois, Kansas, Kentucky, Maryland, Missouri, North Carolina, Oklahoma, South Carolina, Tennessee, Texas, Virginia, and West Virginia, an area corresponding with the distribution of the *Amblyomma americanum* tick.

Patients were between the ages of 5 and 79 (median= 51 years, SD=16) and the majority were white (95%). Slightly more females (52%) than males (48%) were included. For 90% of patients, appearance of a rash was their first symptom. Additional symptoms commonly reported included fatigue or malaise (38%), headache (29%), fever, chills or sweats (14%), and myalgia (14%). Patients were most likely to have a rash on their leg or hip (52%), followed by the abdomen/ flank/ groin (14%) (Table 1).

Patients were most likely to describe the rash as annular (57%), expanding (43%), and with an irregular boundary (41%) (Figure 1). Rash color was commonly reported as the central (bite site) being darker (60%), while others described blanching (31%) and central clearing (22%). Most rashes were described as pruritic (71%).

No tick specimens were provided for identification from the North Carolina cohort. From the CDC direct submission cohort, 27 (57%) had a confirmed Lone Star tick at the site of the tick bite and 2(4.3%) reported a blacklegged tick (*Ixodes scapularis*) (Table 2). The remainder reported an unknown tick and did not submit a photo or specimen to CDC for identification.

Those in the North Carolina cohort were more likely to have an antibiotic prescribed (p=0.01). While specific antibiotic dosage and duration were not consistently captured in the clinical questionnaire, the majority (92%) of those prescribed any medication (n=36) received prescriptions for doxycycline lasting 7 to 21-days.

The range of time between the first and second visits was between 17 and 45 days (median 35 days for NC cohort and 27 days for CDC cohort). At the time of the second visit, a

quarter of participants were still experiencing symptoms (24%). The symptoms most often experienced at the second visit were fatigue/ malaise (15%) and almost half of participants developed central clearing of their rashes (47%) between the first and second visit. By the time of the second visit, only 15% still had a rash.

Antibiotic Effects

A total of 14 individuals were excluded from the analysis of antibiotics and rash duration: nine that did not have a rash observed at the time of the first visit due to delays with seeing a provider, two that were seropositive for Lyme disease, and three that were lost to follow-up after the first visit. Patients that presented with larger rashes (>= 5 cm) at the first visit were more likely to be prescribed antibiotics (p=0.0003). Using a univariate analysis, only antibiotic use had a significant effect (p=0.03) on rash duration. The effects of age, sex, days between visits, other symptoms, and rash size at first visit were not significant. Antibiotic use was significantly associated with shorter rash duration when analyzed using measures from patient and physician reports. Patients that took antibiotics were 6.8 times less likely to have a rash at their second visit as compared with those not taking medication (p=0.02, 95% CI: 1.18-39.25). Only 18% of patients were still experiencing systemic symptoms at their second visit, with no apparent association with antibiotic use (p=0.86). However, when restricting the analysis only to those having confirmed *Amblyomma americanum bites* (n=27), the association between antibiotic use and rash duration was no longer significant.

Laboratory Results

Targeted 16S rRNA metagenomic sequencing in whole blood samples did not detect any tickborne bacteria in the *Borrelia, Ehrlichia, Anaplasma, Rickettsia, Francisella* genera or other known bacterial pathogens.[8]

Discussion:

This study corroborates previously published data regarding signs and symptoms of patients with STARI and provides new information on rash color, shape, and duration. [1,2,5] Due to the similarities of clinical presentations of STARI and Lyme Disease, providers are likely to prescribe similar antibiotic treatments.[6,9] In this analysis, patients who were prescribed antibiotics had a significantly shorter rash duration, though this association was not present when the analysis was restricted to those patients having confirmed *Amblyomma americanum* bites at the site of the rash. Effects observed for the full patient group, including those with unknown tick exposures, could indicate antimicrobials might be helping to inhibit a still unknown or unrecognized bacterial pathogen or that the anti-inflammatory properties of antibiotics may be affecting rash duration.[10] It is important to further evaluate the relationship between antibiotic use and rash duration using a larger sample size and more critical study design, such as a clinical trial, given the potential for side effects and toxicity to the patient with antibiotic use, and to ensure appropriate antibiotic stewardship.

Using targeted V1-V2 16S metagenomic sequencing, no known tickborne or other bacterial pathogens were detected. It is important to consider that most patients did not have their blood drawn until a median of 7.0 days after onset of rash (SD=7.04), which may have limited the ability to find a bloodborne pathogen. Some bacterial pathogens, including *B.*

burgdorferi, the etiologic agent of Lyme disease, are only transient in the blood in the first few days of infection and most often occur at low bacterial loads.[11] It can therefore be difficult to detect bacterial pathogens of this nature in blood with current methods available. This technique has been optimized to detect tickborne bacterial pathogens, thus detections are limited to known pathogens identified against the MiniKraken database and would not include other potential agents, such as viruses, parasites, or any non-infectious components of tick saliva.[8] Ideally, in future studies, rash biopsies or other more specific samples could be included in laboratory testing analyses, which may aid in potentially identifying a pathogenic agent.

Statistically significant differences between the North Carolina and the CDC direct submission cohorts included age, reported comorbidities, likelihood of being prescribed antibiotics, and delays in seeing a provider for the CDC group – which may affect the description of the overall course of illness. Other limitations include the small sample size, not using more comprehensive sequencing methods, volunteer bias among the cohorts, recall bias, and potential measurement bias affecting the rash size reported, making comparisons between clinical presentations of illness less precise. In addition, while only patients who tested seronegative for *B. burgdorferi* were included in this analysis, negative serology and negative nucleic acid testing on blood does not exclude the possibility of early Lyme disease, particularly if the patient received an antibiotic effective against *Borrelia*, or did not mount a detectable antibody response. In conclusion, although an etiologic agent remains unknown for STARI, these results better characterize this condition and suggest that future research on antibiotic treatment and rash duration may be warranted.

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Conflicts of interest:

None.

Disclaimer:

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention (CDC).

References:

1. Symptoms, Diagnosis and Treatment | Southern Tick-Associated Rash Illness (STARI) | CDC. 2018. Available at: https://www.cdc.gov/stari/symptoms/index.html. Accessed 11 May 2022.

2. Wormser GP, Masters E, Nowakowski J, et al. Prospective Clinical Evaluation of Patients from Missouri and New York with Erythema Migrans—Like Skin Lesions. Clin Infect Dis **2005**; 41:958–965.

3. Wormser GP, Liveris D, Nowakowski J, et al. Microbiologic Evaluation of Patients from Missouri with Erythema Migrans. Clin Infect Dis **2005**; 40:423–428.

4. James AM, Liveris D, Wormser GP, Schwartz I, Montecalvo MA, Johnson BJB. Borrelia lonestari Infection after a Bite by an Amblyomma americanum Tick. J Infect Dis **2001**; 183:1810–1814.

5. Masters EJ, Grigery CN, Masters RW. STARI, or Masters Disease: Lone Star Tick–Vectored Lyme-like Illness. Infect Dis Clin North Am **2008**; 22:361–376.

6. Lyme Disease | Tick-borne Diseases | Ticks | CDC. 2020. Available at: https://www.cdc.gov/ticks/tickbornediseases/lyme.html. Accessed 11 May 2022.

7. Ticks, g7382 | MU Extension. Available at: https://extension.missouri.edu/publications/g7382. Accessed 11 May 2022.

8. Kingry L, Sheldon S, Oatman S, et al. Targeted Metagenomics for Clinical Detection and Discovery of Bacterial Tick-Borne Pathogens. J Clin Microbiol **2020**; 58:e00147-20.

9. Erythema migrans rash | Lyme Disease | CDC. 2022. Available at: https://www.cdc.gov/lyme/treatment/erythema-migrans-rash.html. Accessed 8 November 2022.

10. Henehan M, Montuno M, De Benedetto A. Doxycycline as an anti-inflammatory agent: updates in dermatology. J Eur Acad Dermatol Venereol **2017**; 31:1800–1808.

11. Liang L, Wang J, Schorter L, et al. Rapid clearance of Borrelia burgdorferi from the blood circulation. Parasit Vectors **2020**; 13:191.

Table 1: Clinical characteristics of study participants from the University of North Carolina (UNC) and the CDC Direct Submission Cohort – First Visit (n=58)

	UNC Patients N=11 n (%)	CDC Direct Submission N=47 n (%)	Total N=58 n (%)	p-value
First symptom(s)				0.32
Rash	9 (82%)	43 (91%)	52 (90%)	
Another symptom	2 (18%)	4 (9%)	6 (10%)	
Signs and symptoms				
Fatigue/ Malaise	2 (18%)	20 (43%)	22 (38%)	0.18
Headache	3 (27%)	14 (30%)	17 (29%)	1.0
Fever/Chills/ Sweats	1 (9%)	7 (15%)	8 (14%)	1.0
Myalgia	2 (18%)	6 (13%)	8 (14%)	0.64
Nausea	2 (18%)	4 (9%)	6 (10%)	0.32
Anorexia	3 (27%)	3 (6%)	6 (10%)	0.07
Stiff Neck	0 (0%)	5 (11%)	5 (9%)	0.57
Gastrointestinal	2 (18%)	3 (6%)	5 (9%)	0.24
Neck Pain	2 (18%)	2 (4%)	4 (7%)	0.16
Arthralgia	1 (9%)	3 (6%)	4 (7%)	1.0
Lymphadenopathy	0 (0%)	3 (6%)	3 (5%)	1.0
Neurologic*	1 (9%)	1 (2%)	2 (3%)	0.35
Other	0 (0%)	2 (4%)	2 (3%)	1
Rash size observed by physician:				0.063
<5 cm	1 (9%)	13 (28%)	14 (24%)	
5-7 cm	6 (55%)	10 (21%)	16 (28%)	
>7 cm	4 (36%)	14 (30%)	18 (31%)	
Not observed	N/A	10 (21%)	10 (17%)	
Description of rash shape:				
Annular	4 (36%)	29 (62%)	33 (57%)	0.18
Irregular boundary	8 (73%)	16 (34%)	24 (41%)	0.038
Expanding	6 (55%)	19 (40%)	25 (43%)	0.50
Uniformly raised	2 (18%)	13 (28%)	15 (26%)	0.71
Other	0 (0%)	7 (15%)	7 (12%)	0.33
Description of rash color:				
Uniform	3 (27%)	8 (17%)	11 (19%)	0.42
Center (bite site) darker	7 (64%)	28 (60%)	35 (60%)	1.0
Central clearing	3 (27%)	10 (21%)	13 (22%)	0.70
Darker margin	1 (9%)	7 (15%)	8 (14%)	1.0
Blanching	6 (55%)	12 (26%)	18 (31%)	0.079

Description of rash sensitivity:				
Pruritic	9 (82%)	32 (68%)	41 (71%)	0.48
Tender	3 (27%)	14 (30%)	17 (29%)	1.0
Warm to touch**	1 (9%)	11 (23%)	12 (21%)	0.43
Description of other rash characteristics:				
Macular	5 (45%)	8 (17%)	13 (22%)	0.10
Papular	3 (27%)	11 (23%)	14 (24%)	1.0
Vesicular	0 (0%)	3 (6%)	3 (5%)	1.0
Eschar	1 (9%)	0 (0%)	1 (2%)	0.19
Other	3 (27%)	3 (6%)	6 (10%)	0.076
If tick found, how many days before symptom onset?				0.83
After symptoms began	1 (9%)	2 (4%)	3 (5%)	
0 – 3	3 (27%)	20 (43%)	23 (40%)	
4 – 10	2 (18%)	8 (17%)	10 (17%)	
10+	0 (0%)	4 (9%)	4 (7%)	

* Neurologic symptoms reported include dizziness, limb paralysis, difficulty speaking.

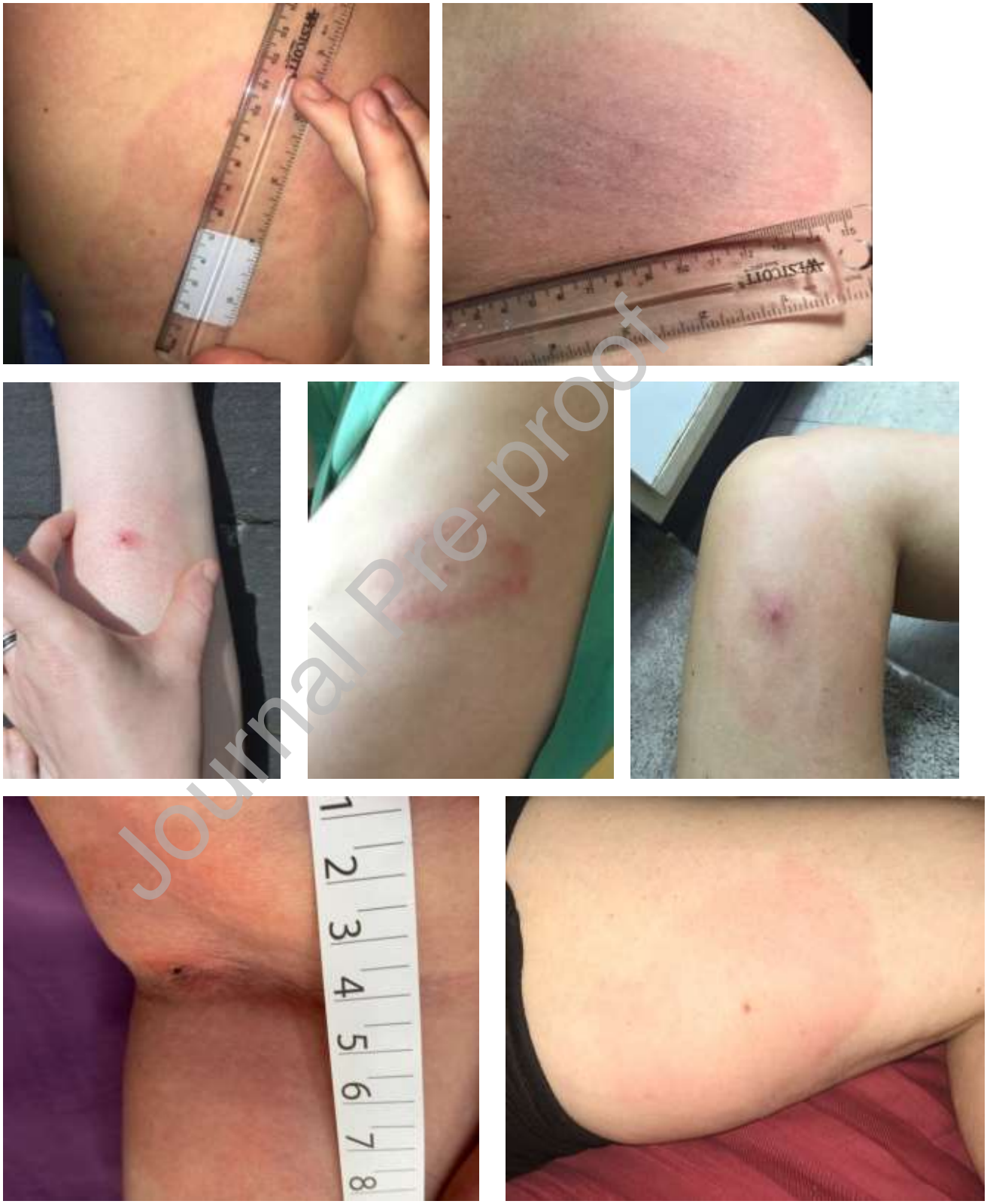
** The original collection form used the term “feverish”.

± Fisher’s exact test used to evaluate the significance of associations between variables with sample sizes <5.

Table 2: Additional characteristics of study participants – First Visit (n=58)

	UNC Patients N=11 n (%)	CDC Direct Submission N=47 n (%)	Total N=58 n (%)	p-value
Age (in years)				0.03
<35	1 (9%)	11 (23%)	12 (21%)	
35 – 55	2 (18%)	22 (47%)	24 (41%)	
>55	8 (73%)	14 (30%)	22 (38%)	
Race/Ethnicity				1.0
White	11 (100%)	44 (94%)	55 (95%)	
Other	0 (0%)	3 (6%)	3 (5%)	
Sex				0.33
Female	4 (36%)	26 (55%)	30 (52%)	
Male	7 (64%)	21 (45%)	28 (48%)	
Presence of multiple rashes				0.61
Yes	2 (18%)	5 (11%)	7 (12%)	
No	9 (82%)	42 (89%)	51 (88%)	
Comorbidities				
Yes	9 (82%)	15 (32%)	24 (41%)	0.0048
No	2 (18%)	32 (68%)	34 (59%)	
Tick attachment status:				
Tick is/ was attached to rash site	7 (64%)	27 (57%)	34 (59%)	1.0
Tick is/ was attached to a site other than the rash site	1 (9%)	1 (2%)	2 (3%)	0.35
Tick was not attached	4 (36%)	17 (36%)	21 (36%)	1.0
Tick attachment status is not known	1 (9%)	2 (4%)	3 (5%)	0.47
Type of tick attached:				0.0001
Lone star tick	0 (0%)	27 (57%)	27 (47%)	
Deer tick	2 (18%)	0 (0%)	2 (3%)	
Unknown	8 (73%)	12 (26%)	20 (35%)	
Not attached	1 (9%)	8 (17%)	9 (16%)	

Figure 1: Example photos of rashes submitted.



CRediT Author Statement

Kristine Lindell: Formal analysis, Investigation, Writing – Original Draft

Sarah Sheldon: Investigation, Validation

Luke Kingry: Investigation, Validation

Paul S. Mead: Methodology, Writing – Reviewing and editing

Claudia Molins: Conceptualization, Methodology, Project administration

Alison F. Hinckley: Formal analysis, Supervision, Writing – Reviewing and editing

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: