

Retrospective Case Reports of Two Central North Carolina Residents: Frequency of Tick Bites and Associated Illnesses, 2001-2014

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BACKGROUND Tick bites are a source of illness and disease agents that may lead to morbidity and occasional fatalities in North Carolina. Public health interest in tick-borne illness and disease has increased due to continuing discoveries of tick-borne diseases and their increasing geographic spread and disease incidence. There are no data published on lay individuals with cumulative tick bites and associated illnesses over a period of years.

METHODS We learned of a married couple living on a central North Carolina property who had used reasonable bite prevention methods, kept attached ticks after removal, and recorded dates and related illness records from 2001–2014. We obtained permission to analyze their records. Ticks were identified by an entomologist.

RESULTS The male subject had a total of 219 bites from identifiable ticks comprising 213 *Amblyomma americanum*, 4 *Dermacentor variabilis*, and 2 *Ixodes scapularis*. He was treated for possible Rocky Mountain spotted fever once and presumed Southern Tick Associated Rash Illness once. The female subject had 193 bites comprising 168 *A. americanum*, 23 *D. variabilis*, and 2 *I. scapularis*. She was treated for 4 episodes of presumed Southern Tick Associated Rash Illness and one possible case of a tick-borne infection. Several years of data were missing for both subjects.

LIMITATIONS This retrospective report relied on the subjects' own records for much of the data. The experience of these individuals cannot be generalized. Diagnoses of these tick-related illnesses are inexact due to lack of tests for the Southern Tick Associated Rash Illness and cross-reactivity in tests for spotted fever rickettsiosis.

CONCLUSIONS This report demonstrates that tick-associated illnesses, including episodes fitting the Center for Disease Control and Prevention's definition of the Southern Tick Associated Rash Illness, may be more common than realized. Use of personal tick protection measures for tick bite illness and disease prevention may not be sufficiently protective. Further subject-based research on tick and disease burden on selected populations would be informative, and could aid in planning appropriate actions to mitigate the effects of tick-borne disease in North Carolina.

Public health interest in ticks parasitizing humans has increased sharply in response to the continuing recognition of emerging tick-borne diseases and the geographic spread of human-biting ticks. The predominant human-biting tick in the North Carolina Piedmont is the lone star tick (*Amblyomma americanum*) while less common species include the American dog tick (*Dermacentor variabilis*) and the blacklegged (deer) tick (*Ixodes scapularis*) [1]. All these ticks are known to be potentially infected with a variety of bacterial [1-3] and viral human pathogens [2-5]. Reportable tick-borne illnesses, a considerable source of illness and occasional fatalities in North Carolina [6, 7], include Lyme disease, spotted fever rickettsiosis (SFR) (formally Rocky Mountain spotted fever [RMSF]), ehrlichiosis, anaplasmosis, and tularemia. Tick-borne illness cases that meet reporting requirements generally represent only a minority of the disease burden actually occurring [8, 9]. The enigmatic Southern Tick Associated Rash Illness (STARI) [2, 3, 10] is not included in counts as its cause is still unknown; therefore, no test for it exists and there are no reporting requirements. As of 2015, 6 North Carolina counties are endemic for Lyme disease according to the Centers for Disease Control

and Prevention (CDC) 2011-2016 standards for establishing local acquisition, including two Piedmont counties, Wake and Guilford. No pathogenic tick-borne viruses have been reported in humans to date in North Carolina.

There are few prevalence data on laypersons with tick bites and resultant illnesses. A recent CDC survey found 25.4% of South Atlantic residents reported tick exposure in their household in the past year; 11.7% sought medical care [11]. A Georgia study examining 597 ticks submitted by 444 participants found 12 individuals fit requirements for possible tick-borne illnesses [12]. We could not find any retrospective reviews of tick bites and illness experience among lay individuals over time anywhere in the United States. We describe the 14-year experience of two North Carolina individuals from 2001 through 2014.

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Materials and Methods

Subjects and Institutional Review Board Status

We learned of a married couple who had lived at the same place since 1997, had tick-associated illness records since that year, and who kept their attached ticks from 2001 through 2014. Exposure was not constant due to occasional travel. Both individuals gardened only within a fenced area. Pets included 1-3 outdoor cats treated as needed with topical tick and flea deterrents.

The University of North Carolina Center for Bioethics determined that this retrospective case study did not need to be assessed by the institutional review board as no identifiers are included. We obtained signed consent from the subjects to have the ticks identified, analyze the records of their bites, obtain medical records for tick-related visits, and publish the findings.

Site Description

The residents' county is comprised of suburban neighborhoods and farmland, with most of the population residing outside the county's several small towns. The subjects resided on a multiacre property with mixed hardwood trees on the rear portion of the property, which sloped to a creek; pine trees stood in the acreage near the paved access road. An acre and a half of open area for the house, lawn, and gardens was surrounded by an 8-foot high deer fence, which had been in place since 1997. The hardwood understory was leaf litter with *Microstegium vimineum* (Japanese Stiltgrass) and shrubs. The pine understory was comprised of pine needles, low shrubs, small hardwoods, vines, and *M. vimineum*. Several hundred uninhabited acres lay behind the small subdivision where the subjects live. The entire county is known for high deer density and is highly infested with lone star ticks along with occasional dog and black-legged ticks [1]. Acaricides, pesticides that kill ticks and mice, were not used on the property.

Tick Identification, Collection, and Medical Records

The subjects taped attached ticks on index cards after removal, noting the date and body location. If an illness or rash occurred following a tick bite, they saw their prospective medical providers and kept records of dates, diagnoses, prescriptions, and photographs of any rashes. Medical records were requested at the end of the 2014 collection period. Only attached ticks from their property are included in this report. The life stage and species of ticks were keyed [13-16] and identified under microscopy by a former state entomologist at the end of the collection period.

Tick Prevention Methods

Both subjects used CDC recommended tick prevention, including wearing permethrin-treated clothing for long outdoor sessions and safe removal methods, [17, 18] with several exceptions. Changing into treated clothing and

showering after every short outdoor exposure was not practical because of these frequent, often daily, occurrences. They used N,N-diethyl-meta-toluamide (DEET) or other recommended repellents when indicated by season and tick activity and conducted full body tick checks at least once a day. The subjects knew that lone star tick bites cause a normal inflammatory reaction including erythema and intense itching (see Figure 1). Often the itching led to their finding attached ticks.

Results

Tick Data

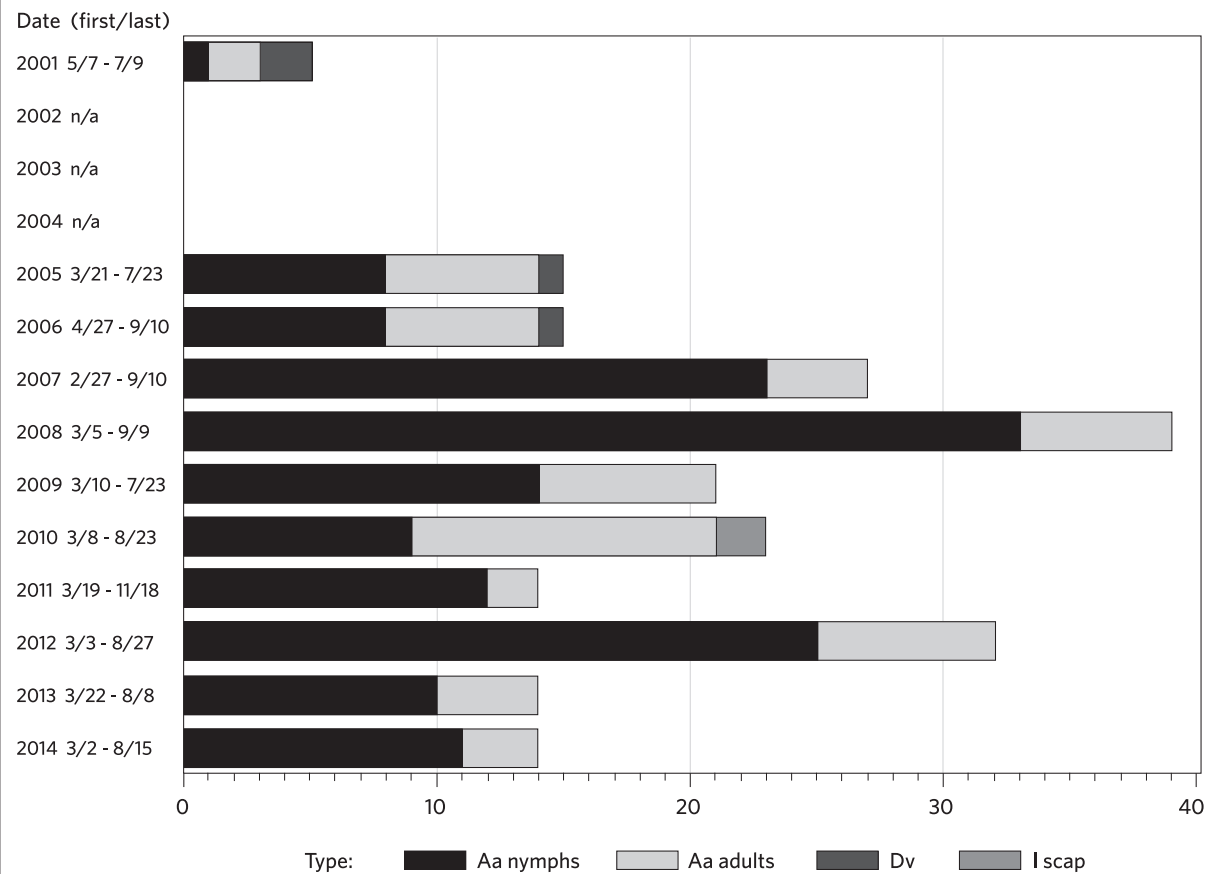
Cards from the male subject for years 2002-2004 were missing. In 2001 and 2005 through 2014, the male subject had a total of 219 tick bites, comprised of 213 lone star ticks (61.7% nymphs), 4 American dog ticks, and 2 blacklegged ticks (1 nymph and 1 female) (see Figure 2). From 2001 through 2014, he was treated for possible RMSF (2007) and presumed STARI (2010). No illnesses attributable to NC tick exposure occurred during the period 2002-2004, although a case of Lyme disease was contracted while visiting Maine. The female subject's cards for 2005 and 2007 were missing. Although scanned copies were available, the images of the ticks were not of sufficient quality to allow for identification of all the tick species. For the years 2001-2004, 2006, and 2008-2014, the female subject's 193 bites were comprised of 168 lone star ticks (66.7% nymphs), 23 American dog ticks, and 2 blacklegged nymphs (see Figure 3). She had one episode of an *erythema migrans*-like (EM) rash developing at the site of a lone star tick bite in 2006, 2007, 2012, and 2013. She had one other illness without an EM-like rash following a lone star tick bite in 2008. For both subjects, a portion of nymphal *A. americanum* ticks were partially engorged before being found and removed. Additionally for both subjects, most lone star tick

FIGURE 1.

A lone star tick bite showing a typical reaction. The nymphal tick still attached. The lesions usually cause intense pruritus and last one to two weeks. This 'normal' reaction is to be distinguished from the *erythema migrans*-like rash that sometimes develops.



FIGURE 2.
Male Resident: Number of Tick Bites by Species, Life Stage, Dates of First and Last Known Tick Bite, and Year



Note. Totals: Aa adults 59, Aa nymphs 154, Dv 4, I scap 2.
 Larval Aa tick bites, not shown, occurred in 2005, 2006, and 2008, 2009, and 2012, usually in the fall.
 Aa = *Amblyomma americanum*, Dv = *Dermacentor variabilis*, I scap = *Ixodes scapularis*

bites showed only the normal inflammatory reaction lasting 1 to 2 weeks (see Figure 1).

For purposes of this report, and as described by the CDC, STARI is defined as an expanding EM-like rash up to 8 cm or more, distinct from the normal smaller pruritic rash at the site of a known *A. americanum* bite, with or without Lyme-like symptoms. The rash is similar to the EM rash of Lyme disease, follows the bite of the lone star tick, usually begins within 7 days, and may be accompanied by Lyme-like symptoms such as fatigue, fever, headache, and muscle and joint pains [19, 20]. The case reports follow.

Tick-associated Diseases

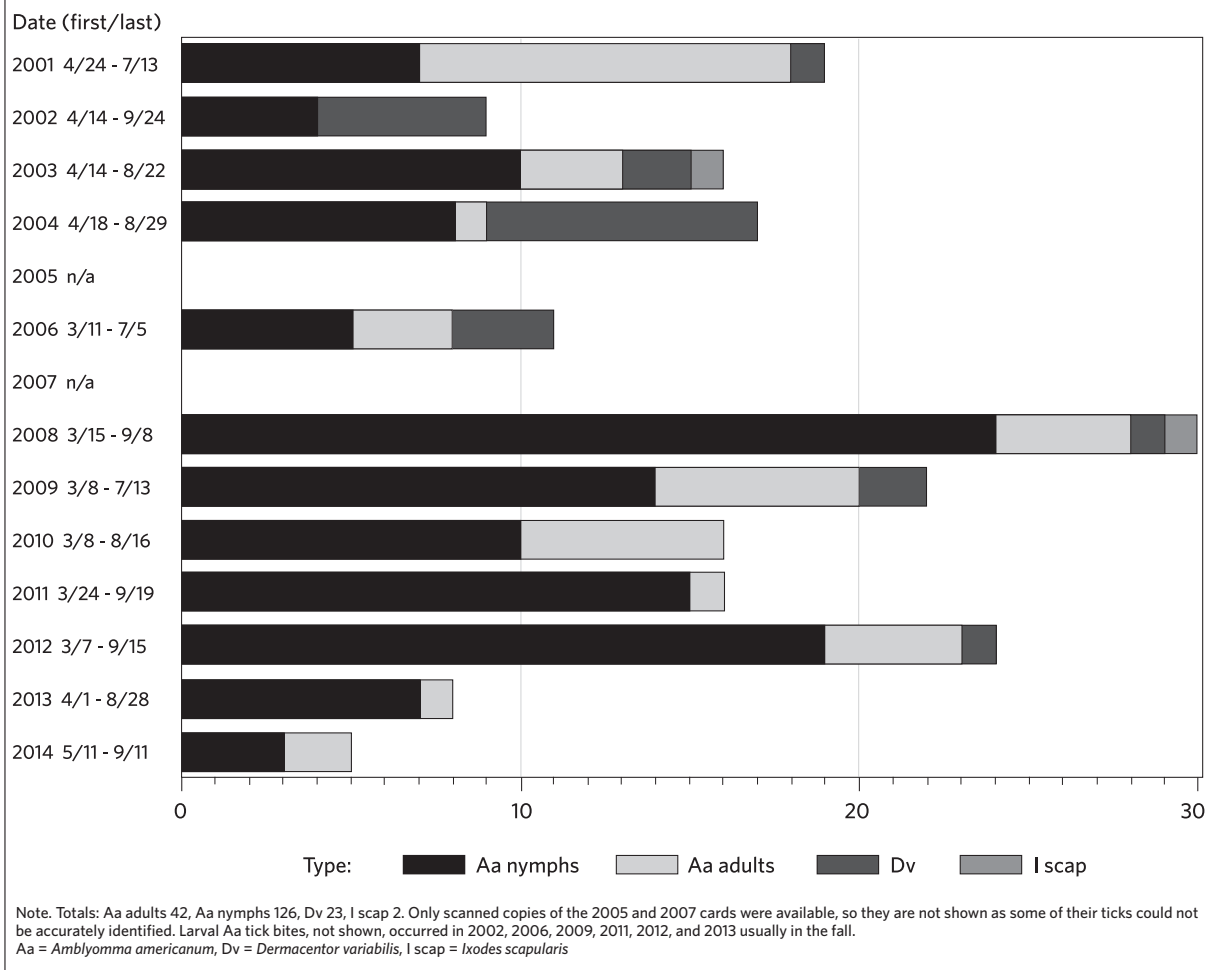
Male Subject

Illness 1, 2007. All known attached ticks were *A. americanum*. The last known bite the subject received before becoming ill 5 weeks later was from a nymph and occurred one day before the subject left for Alaska. He returned in mid-October feeling well, but became ill a few days later. According to the medical record, the patient complained

of headache, fever, chills, photophobia, fatigue, anorexia, myalgia, and shaking chills. His blood pressure standing was 90/50. The patient was noted to appear quite ill, and hospitalization was considered. No rashes were present. A tick-borne infection was suspected, and 100 mg of doxycycline twice a day for two weeks was prescribed. Labs comprised a complete blood count, a metabolic panel, assays for *Ehrlichia* and RMSF, and a Lyme IgM/IgG enzyme-linked immunosorbent assay. At the three day follow up, the patient reported rapid improvement within 36 hours after starting doxycycline. LabCorp results, not available until after the second visit, were all normal except the RMSF assay of 13 Panbio units (normal 0-8 units). Platelets were 192x10E3/uL (normal 140-415x10E3/uL). The patient recovered fully.

Illness 2, 2010. The subject developed an expanding EM-like rash in March 2010 after he removed a nymphal *A. americanum* from his right thigh. He had no other symptoms. In the medical record, a physician described the rash as a "5 cm raised pink lesion without central clearing" (see Figure 4) and noted "possible early erythema migrans

FIGURE 3.
Female Resident: Number of Tick Bites by Species, Life Stage, Dates of First and Last Known Tick Bite, and Year



from STARI.” He prescribed 100 mg of doxycycline twice a day for 2 weeks. The rash cleared and the patient recovered fully. This illness fits the CDC definition of STARI.

Female Subject

Illness 1, 2006. After arriving in London in July 2006, the subject found an unengorged embedded female lone star tick on her left medial thigh. By the next day, a circular rash at the attachment site developed and because it continued to expand, she sought emergency care by which time the nonpruritic rash was 12 cm longitudinally. She had no other symptoms. Doxycycline, 100 mgs twice a day for 10 days, was prescribed. Only the patient’s personal records were available. The rash resolved rapidly, and the patient recovered fully. This illness fits the CDC definition of STARI.

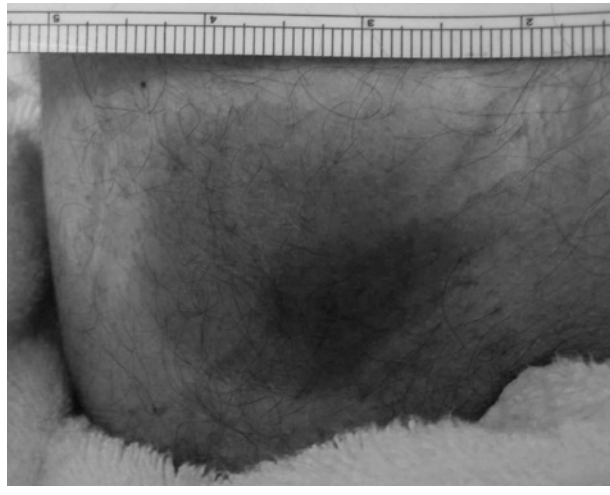
Illness 2, 2007. Although the original card showing attached ticks for 2007 was lost, a scanned copy was available as were medical notes for an EM-like rash in June. The subject removed two presumed nymphal lone star ticks from her right groin. Four days later, an expanding rash developed

at one bite site, stopping at just under 5 cm. One week later, due to dizziness and pressing chest pain, she saw her internist who prescribed 400 mg doxycycline twice a day for one week, then 100 mg twice a day for 3 weeks. LabCorp tests for RMSF, *Babesia microti*, and an IgG Lyme Western Blot (WB) were negative. The IgM Lyme WB showed only a reactive 23-kDa band, which is negative for Lyme disease by the CDC case definition. The patient recovered fully. This illness fits the CDC definition of STARI.

Illness 3, 2008. In August 2008, the subject removed a tick from her left buttock. No rash developed, but the patient felt sick (details not recorded) after a few days. The patient’s physician prescribed doxycycline twice a day for 10 days for a presumed tick-borne illness. She fully recovered. The medical record was not available as it was destroyed by accident when her internist closed her practice.

Illness 4, 2012. In May 2012, the subject removed a lone star nymph from her right medial thigh. Two days later, she saw her new medical provider because of an expanding EM-like rash (see Figure 5) and dizziness. The patient

FIGURE 4. *Erythema migrans*-like rash developing on the male subject following removal of a nymphal lone star tick in 2010 from his right thigh, consistent with STARI. The ruler is in inches and shows a diameter of 2.5 inches or approximately 6 cm.



was prescribed 100 mg of doxycycline twice a day for 21 days. The 5 cm rash resolved quickly (see Figure 5b), and the patient had no further dizziness. This illness fits the CDC definition of STARI.

Illness 5, 2013. In July 2013, the patient removed an embedded lone star nymph from her right calf. Two days later, an expanding erythematous rash developed, and at approximately 5 cm she saw her medical provider. No other signs or symptoms were noted. She was prescribed 21 days of doxycycline, 100 mg twice a day. The rash resolved quickly and the patient remained well. This illness fits the CDC definition of STARI.

Discussion

This 14-year experience with tick bites and incidence of tick-associated illnesses, primarily STARI, of two tick-aware individuals at their residence in a central, rural area of North Carolina is the first occurrence of recorded duration to our knowledge. The subjects limited their exposure to ticks during the March through October tick season by standard prevention methods as were practical and by staying within a deer fence that surrounded their house and gardens. Even so, in 24 person-years, the individuals together had 412 identifiable nymph or adult attached ticks and 7 associated illnesses, comprising one case of possible RMSF or other SFR, 5 of presumed STARI, and 1 undiagnosed illness thought to be of tick-borne origin. The couple's numerous larval *A. americanum* bites are not included in these counts. Thus, 1.7% of the attached ticks were associated with presumed tick-related illness. Interestingly, the Georgia study with 597 ticks from 444 people found 2.7% developed a possible tick-borne illness [12]. The risk of presumed STARI varied considerably between the subjects even though each experienced a similar number of lone star tick bites. The male

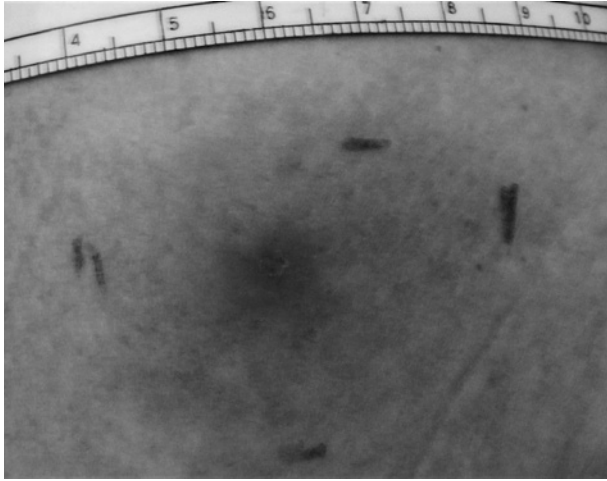
subject also had 2 tick-borne illnesses not included because they occurred outside the report dates or were contracted in another location. Two years prior to this study period, he was diagnosed and treated for RMSF, based on symptoms and RMSF titers. It is possible that this earlier episode could have accounted for the positive RMSF test in 2007. In addition, it is well known that tests for RMSF cross-react with other spotted fever group (SFG) species [21], therefore, an etiology assigned to a specific *Rickettsia* species cannot necessarily be inferred from a positive serologic test. The 5 weeks between exposure and onset of symptoms is longer than the known incubation period for rickettsial diseases. He may have had an unnoticed tick bite on his return home. His symptoms were consistent with RMSF or another SFG rickettsiosis as was his brisk response to treatment. In 2002, he had developed a classic EM rash on his trunk while returning from an area in Maine highly endemic for Lyme disease. He was treated for Lyme disease and had no further symptoms. The treating physician no longer had either of these records. The female subject had not had any tick-related illnesses other than the five described above.

Although tick populations are dynamic, and the risk of contracting disease is highly variable [3] due to factors such as individual susceptibility and exposure, the results of this study are an indicator of the substantial nuisance and potential disease exposure, especially where lone star tick populations have increased. This occurred even though the subjects attempted to limit their exposure to ticks by following CDC-recommended prevention measures as practical. Numerous studies have documented the ascendancy of *A. americanum* ticks across the Southeast, their extension as far north as Massachusetts as early as 1947 [20, 22], and more recently into Maine and west to Nebraska [3, 23, 24]. Lone star tick pathogens include the long-implicated *Rickettsia rickettsii*, the agent of RMSF [25, 26]; *Francisella tularensis*, the agent of tularemia; *Ehrlichia chaffeensis*, *Ehrlichia ewingii*, Panola Mountain Ehrlichia; [3] and other rickettsial organisms including *R. parkeri* and *R. amblyommii* [3]. The latter is now suspected of being a mild pathogen and may contribute to cross-reactivity when testing for *R. rickettsii* [3, 27]. A newly identified lone star tick-vectored virus commonly called Heartland virus has caused 2 deaths and 5 other cases in the Midwest and South [28]. More *A. americanum* viruses are being identified [4, 5]. The recently described lone star tick-associated mammalian meat allergy is an increasing problem [29, 30]. Lone star tick related diseases and conditions might be higher were it not for the usual intense pruritus at the attachment site which likely leads to immediate removal of the tick. The proportion of persons sensitive to the saliva of lone star ticks is very high [31].

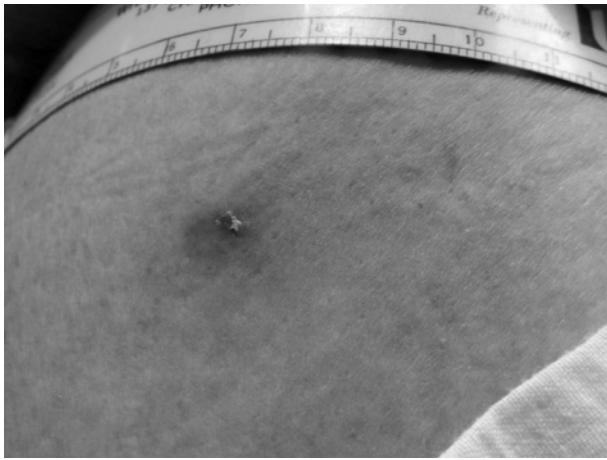
A. americanum is also well-known as the tick-vector associated with STARI, sometimes called Masters disease [32]. Data on its incidence are entirely lacking, in part because there is no test or diagnostic code [33, 34], and the public has not been trained to keep attached ticks. Without know-

FIGURE 5A AND 5B.

(a) *Erythema migrans*-like rash developing at the site of a female lone star bite following removal from the patient's right medial thigh two days prior, May 2012. The patient saw her physician after episodes of dizziness and expansion of the rash.



(b) The EM rash 20 hours post doxycycline therapy.



ing that a patient with an EM-like rash, with or without other Lyme-like symptoms, was bitten by a lone star tick at the rash site, STARI cannot be diagnosed with certainty. The etiology is still being investigated. One report suggested that *R. amblyommii* could be the cause of STARI, but the description of the rash did not seem consistent with EM; no photograph was included, and only one case was presented [35]. A Georgia study [12] reported EM rashes on two persons bitten by lone star ticks positive for *R. amblyommii*, but this does not preclude the rashes being caused by another agent. After several papers in the early 2000s looked at whether the then recently discovered *Borrelia lonestari* was the cause of STARI [19, 36], that possibility has been largely dropped [3, 19], although more investigation has been suggested [2]. What is now termed STARI was first described in adolescents attending a summer camp in the North Carolina Piedmont [37]. As with several other studies on STARI, it is notable

that some subjects had positive enzyme-linked immunosorbent assays and some positive bands on immunoblots for *B. burgdorferi* [32, 37-39]. Interestingly, the female subject in this report had a reactive IgM 23-kDa band following one episode of presumed STARI (illness 2). The CDC states that STARI has not been linked to arthritis, neurologic disease, or chronic symptoms [19]; however, Masters and colleagues have published evidence that sequelae do occur [32, 38].

Unfortunately, any conclusions from STARI studies must be tempered as some studies have not been able to confirm that all patients had an EM-like rash due to the bite of a lone star tick. Knowing whether the tick related to the EM rash was a lone star tick is important since *I. scapularis* and *A. americanum* have been sympatric in the North and Southeast for many years, and the EM rashes caused by each are indistinguishable among individuals [40]. In addition, long-term studies of untreated STARI patients have not been conducted, so lack of long-term effects from STARI should not be assumed. Due to today's progressive standards for informed consent, such studies may be difficult or impossible to conduct since they would require a cohort of patients agreeing to no treatment over time in the face of existing evidence of Lyme-like symptoms associated with STARI [33]. Most reports support treating these patients as for Lyme disease [41-43], though some question whether treatment is needed in spite of the condition's Lyme-like symptoms [44]. A recent study suggests that in the South, some cases of Lyme disease-like illnesses may be attributable to lone star tick-vectored infections with previously undetected *B. burgdorferi sensu lato* [45], but more research is needed to confirm these findings. A subsequent study by Stromdahl, et al. concluded *A. americanum* do not contain Lyme-group *Borrelia* [46]; however, a study subsequent to that one by Rudenko, et al. found evidence of occasional *B. burgdorferi* in *A. americanum* ticks [47]. Establishing consistent diagnostic and reporting criteria is challenging due to the numerous variables and uncertainties affecting ticks as vectors of human disease and conditions.

During the latter years of this report period, in the area where the subjects lived, Smith et al. [1] found the predominant questing tick to be the lone star tick, comprising 98.5% of their collection of 3746 ticks, followed by the American dog tick at 1.0%, and the black-legged tick at 0.4%. *Rickettsia* spp. were detected in 68.2% of *A. americanum* with 56.4% identified as *R. amblyommii*. Other organisms comprised *Ehrlichia chaffeensis* (1.8%) and *B. lonestari* (0.4%). Of *D. variabilis* collected, 19.4% were positive for *R. montanensis*, 11.1% for *R. amblyommii*, and 13.9% with unidentified SFG rickettsiae. Of the small number of *I. scapularis* collected, 40% were positive for *B. burgdorferi sensu lato*. The subjects' lack of American dog tick bites in the latter years of the study period is consistent with the documented decline of *D. variabilis* [2, 3]. Although the subjects' exposure to these local pathogens was similar, their presumed tick-borne illnesses were not. Individual susceptibility to infections influ-

ences the incidence of tick-borne illnesses in persons living in an endemic area.

This report has several important limitations. The data are based on the voluntary collections of just 2 individuals over a 14-year period; therefore, the findings from their records cannot be independently ascertained. They may not represent a typical Piedmont exposure and illness history nor are they generalizable. However, the data do provide two peoples' experience of nuisance and presumed tick-borne illness risk over a number of years. The male subject's RMSF diagnosis cannot be verified due to the cross-reactivity of antibodies to spotted fever group rickettsiae [21], which causes challenges in categorizing the specific SFG species that caused the immune response as well as the lack of convalescent serum. Though STARI lacks a specific test, in every case where the subjects developed an EM-like rash, it occurred at a lone star tick attachment site and fit the CDC's definition for the condition [19]. Some of the medical records were destroyed either on purpose or accidentally by the treating medical providers, but the subjects had their own records of prescriptions and illness notes. While the resolution of EM-like rashes and symptoms following antibiotic treatment is associated with treatment [32, 37], it does not prove a tick-related cause because resolution without treatment is known to occur in both Lyme disease and STARI.

Conclusions

This is a first report of the tick parasitism and presumed tick-borne illness experience, including STARI, over many years of two people living where species of human-biting ticks may carry several human pathogens. In spite of the subjects' practical use of prevention methods, they still experienced a high number of bites, discomfort, and associated illnesses, especially presumed STARI. In North Carolina, the state entity which was charged with informing and protecting the public from pests like ticks and mosquitoes and which conducted research to aid their mission, was dismantled in 2011 as a money-saving strategy [48]. The public has largely been left on their own to avoid ticks and bite sequelae. This report suggests that reliance on citizens using personal tick protection measures may be inadequate. Fortunately, in early 2017, the state Department of Health and Human Services hired two medical entomologists, one of whom will focus on ticks.

Exposure to ticks in North Carolina is widespread and some undiagnosed illnesses associated with tick bites could be due to new emerging pathogens [1-3]. As studies have documented, ticks and the pathogens they may carry are increasing in numbers and range [3]; it may be time to initiate planning to mitigate this expanding public health problem. Population-based research could inform health care providers, public health practitioners, and policymakers. Understanding risk and building consensus for diagnosis, reporting, and best practices for protecting the public from ticks and their sequelae would be a starting point. NCMJ

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