

# THE ASCENDANCY OF *AMBLYOMMA AMERICANUM* AS A VECTOR OF PATHOGENS AFFECTING HUMANS IN THE UNITED STATES\*

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■ **Abstract** Until the 1990s, *Amblyomma americanum* was regarded primarily as a nuisance species, but a tick of minor importance as a vector of zoonotic pathogens affecting humans. With the recent discoveries of *Ehrlichia chaffeensis*, *Ehrlichia ewingii*, and “*Borrelia lonestari*,” the public health relevance of lone star ticks is no longer in question. During the next 25 years, the number of cases of human disease caused by *A. americanum*-associated pathogens will probably increase. Based on current trajectories and historic precedents, the increase will be primarily driven by biological and environmental factors that alter the geographic distribution and intensity of transmission of zoonotic pathogens. Sociologic and demographic changes that influence the likelihood of highly susceptible humans coming into contact with infected lone star ticks, in addition to advances in diagnostic capabilities and national surveillance efforts, will also contribute to the anticipated increase in the number of recognized cases of disease.

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## INTRODUCTION

Until relatively recently, the lone star tick, *Amblyomma americanum* (L.), was regarded as the pathogen-poor relative of the other common species of human-biting ixodid ticks inhabiting North America (125). Despite its distinction as the first tick to be described in the United States in 1754 and its reputation as a major pest to humans and livestock (62), the lone star tick's position as principal vector for any human disease was not convincingly demonstrated until the early 1990s.

*Dermacentor variabilis* in the eastern United States and *Dermacentor andersoni* in the western United States held principal claim for the transmission of *Rickettsia rickettsii* (20), the etiologic agent of Rocky Mountain spotted fever (RMSF), the most commonly fatal tick-borne disease in the Western Hemisphere. Similarly, *Ixodes scapularis* in the eastern and north-central United States and *Ixodes pacificus* in the western United States were firmly established as the principal vectors of *Borrelia burgdorferi* (78), the etiologic agent of Lyme disease, the most frequently reported vector-borne disease in the United States. In contrast, the primary human and veterinary health concerns regarding *A. americanum* were founded upon its aggressive and nondiscriminatory biting habits at all life stages, resulting in its notorious reputation as a nuisance species (13, 62).

There have been several occasions when *A. americanum* appeared to be the natural suspect in situations involving outbreaks or sporadic occurrences of human disease in which other tick vectors could be effectively eliminated. The most famous of these outbreaks was the mysterious "Bullis fever" that swept through a company of soldiers, stationed at Fort Sam Houston, who had participated in maneuvers at Camp Bullis, Texas, during the spring of 1942. Over 1000 cases of an acute febrile illness, accompanied by severe headache, marked lymphadenopathy, weakness,

nausea, and vomiting, developed among the soldiers, all of who had received multiple tick bites during the days preceding their illness (148). At the time of hospitalization, several of the ill soldiers still had ticks attached to them that were identified as lone star ticks. James M. Brennan, a medical entomologist who investigated the site, commented about the innumerable abundance of lone star ticks: "The writer could find no records in literature, through correspondence, or from verbal information, of a greater concentration of this species elsewhere in the United States" (17). Brennan noted that on July 24, 1943, four men collected 4086 adult *Amblyomma* from a single location without moving (17). Serologic and animal inoculation tests ruled out *Coxiella burnetii* (the agent of Q fever), *R. rickettsii*, and *Rickettsia typhi* (the agent of murine typhus) as causes of Bullis fever (148). Rickettsiae were reported to have been isolated from the blood and lymph nodes of patients with Bullis fever and from emulsions of *A. americanum* (4). The putative agent of Bullis fever was named "*Rickettsia texiana*" (4), although no isolate exists today. Bullis fever apparently vanished after 1943; however, speculation about the nature of the causative agent continues (58). The lone star tick would have to wait another 50 years to unequivocally obtain principal vector status for an infectious agent of humans.

In this review we focus on the accumulating data that incriminate *A. americanum* as an important vector of zoonotic pathogens of humans, in particular, concentrating on the *Amblyomma*-associated ehrlichioses. We summarize information on the population dynamics of this tick and how its geographic distribution and population density have been influenced by corresponding changes occurring among its principal vertebrate hosts. Last, we describe a variety of additional factors that have contributed to the increasing recognition of the public health significance of human diseases associated with this tick and speculate on future trends in the incidence of disease.

## NATURAL HISTORY OF *AMBLYOMMA AMERICANUM*

*A. americanum* is a three-host, non-nidicolous tick distributed from west-central Texas, north to Iowa, and eastward in a broad belt spanning the southeastern United States. Along the Atlantic Coast, the range of this species extends through coastal areas of New England as far north as Maine (71). Sustainable lone star tick populations may also occur or exist transiently in foci well outside their well-established range. Historical records (64) and isolated reports of lone star ticks from western and upper-midwestern states (95) could reflect established regional populations or ticks unintentionally transported on humans with a recent history of travel.

*A. americanum* is found predominantly in woodland habitats, particularly young second-growth forests with dense underbrush (62). The abundance of lone star tick populations is influenced largely by the availability of suitable animal hosts for the life stages of the tick and by the availability of habitats with physiographic features that offer protection for hosts and guard against desiccation of the tick. In this context, white-tailed deer represent a preeminent host for *A. americanum* because they

provide blood meal sources for all three stages of *A. americanum* and generally deposit engorged ticks in wooded habitats that maximize tick survival (99). Lone star ticks are aggressive nonspecific feeders and bite humans at all three stages. Similarly, few mammals or birds are exempt as potential hosts for one or more stages of this tick. Adult *A. americanum* feed on medium- and large-sized mammals, and larvae and nymphs infest various ground-feeding birds, medium- and large-sized mammals, and, on occasion, small mammals (76). Although the host range for lone star ticks is vast, *A. americanum* exhibits considerable dependence on larger wildlife species as hosts. A parameter to quantify the relative qualities of a host for *A. americanum* ticks seeking a blood meal was developed by Mount et al. (99) as the base- or intrinsic host-finding rate. These rates were derived from published values and varied with the size, habits, attractiveness, and suitability of a particular host for tick feeding and as rates specific to tick stage. Estimates of the intrinsic host-finding rates for larval ticks are estimated to be >20-fold higher for white-tailed deer than for small mammals and birds and >5-fold higher for white-tailed deer than for medium-sized mammals (99). Intrinsic host-finding rates for adult lone star ticks are even more disparate and are estimated to be >400-fold higher for white-tailed deer than for medium-sized mammals (99). These data suggest that in the absence of large mammalian hosts, *A. americanum* populations will decline and densities of ticks on medium-sized mammals and birds will also diminish (99).

Within their geographic range, lone star ticks are often the most common tick submitted for identification or reported by humans parasitized by a tick. When newspaper advertisements and public awareness posters in Georgia and South Carolina from 1990 through 1995 solicited tick submissions, 83% ( $N = 913$ ) of the submitted ticks were *A. americanum*, including 231 adults, 262 nymphs, and 265 larvae (52). In an investigation that provided an epidemiologic link between *A. americanum* and an erythema migrans-like rash illness in North Carolina, 97% ( $N = 588$ ) of the ticks collected from vegetation and 95% ( $N = 197$ ) of the ticks attached to humans were lone star ticks (72).

Adult and nymphal lone star ticks are generally most active during April through June and decline markedly in abundance and activity as summer progresses (36, 62). The early-season activity of adult and nymphal ticks, which precedes that of larvae, increases the probability of acquisition of a pathogen by larval ticks at the first blood meal. *A. americanum* overwinters as replete larvae, unfed or replete nymphs, or unfed adults (62).

## BACTERIA (OTHER THAN EHRLICHIAE) ASSOCIATED WITH *AMBLIOMMA AMERICANUM*

Various bacteria have been isolated or detected from *A. americanum* (Table 1). At least five are agents of disease in humans. Some of the bacteria listed in Table 1 have been isolated only from ticks (e.g., WB-8-2 and MOAa agents) and are of unknown pathogenicity in humans. Others are believed to cause human infection on the basis of serologic reactivity to their specific antigens [e.g., 85-1034, "R.

**TABLE 1** Bacteria isolated or identified from *Amblyomma americanum*

Bacterial agent	Disease in humans	Comments	Reference
<i>Ehrlichia chaffeensis</i>	Human monocytic ehrlichiosis (HME)	The most severe of the three ehrlichioses of humans in the United States. Underreported and probably as common as Rocky Mountain spotted fever.	(2, 53)
<i>Ehrlichia ewingii</i>	<i>E. ewingii</i> ehrlichiosis	Most commonly diagnosed in immunosuppressed persons. Less than 20 cases documented.	(19, 108)
<i>Rickettsia rickettsii</i>	Rocky Mountain spotted fever	Role of lone star ticks in transmission is uncertain, as recent surveys have not identified <i>R. rickettsii</i> in ticks.	(59, 113)
<i>Coxiella burnetii</i>	Q fever	Tick transmission is not thought to play a significant role in human disease, although many species of ticks are naturally infected.	(32, 113)
<i>Francisella tularensis</i>	Tularemia	Tick transmission remains important in endemic occurrence. Other routes of transmission, such as direct contact with wild rabbits, are also significant.	(66, 136)
" <i>Borrelia lonestari</i> "	Probable cause of southern tick-associated rash illness	Likely to become recognized as a common disease where lone star ticks exist in high numbers. Agent as yet uncultivable.	(9, 70)
85-1034 ("Rickettsia amblyommii")	Possible mild spotted fever rickettsiosis	Association with human disease based on serologic reactivity only.	(33)
<i>Rickettsia parkeri</i>	None described	Originally isolated from <i>Amblyomma maculatum</i> in Texas.	(59, 112)
WB-8-2	None described	Nonpathogenic or mildly pathogenic in guinea pigs and meadow voles. Most closely related to MOAa and <i>Rickettsia montana</i> .	(22, 146)
MOAa	None described	Most closely related to WB-8-2 and <i>Rickettsia montana</i> .	(146)

*amblyommii*" (33)] or on the basis of identification of presumed pathogen DNA in samples from clinically ill persons [e.g., *Borrelia lonestari* (70)].

### *Francisella tularensis*

The potential link between a tick vector and the transmission of *Francisella tularensis* was first recognized in the late 1940s in Arkansas where it became apparent that most tularemia cases were occurring from April through September, when rabbit

hunting and direct contact with rabbits was rare but tick bites were common (145). In the early 1950s, *F. tularensis* was isolated from lone star ticks collected from Arkansas (66). Although the prevalence of *F. tularensis* among field-collected *A. americanum* ticks was low, estimated at 0.04% among ticks from Arkansas (1.9% of 576 pools of lone star ticks composed of 28,661 individuals were positive), investigations suggested that ticks were involved in the transmission of tularemia to dogs and potentially to cattle (23). Transstadial transmission of *F. tularensis* was subsequently demonstrated by experimental infection of *A. americanum* (65). Tick bite continues to be strongly associated with the occurrence of tularemia in the United States. In a series of 1026 cases of tularemia reported from 1981 to 1987 from Arkansas, Kansas, Louisiana, Missouri, Oklahoma, and Texas, 63% of cases reported an attached tick, while only 23% had exposure to rabbits (136).

### *Rickettsia rickettsii*

Data linking *A. americanum* to the transmission of *Rickettsia rickettsii* and this tick's involvement in the epidemiology of RMSF in humans are largely circumstantial (57). The first guinea pig isolations of a spotted fever group rickettsiae (SFGR) believed to be *R. rickettsii* were made in Texas in 1942 from samples collected from two fatal cases of spotted fever occurring at a location heavily infested by lone star ticks, specimens of which were submitted by the family of the decedents (5). The esteemed rickettsiologist R.R. Parker recovered rickettsiae he identified as *R. rickettsii* from unfed *A. americanum* nymphs collected from Oklahoma in 1942 (113). Other investigators reported that emulsions produced from lone star ticks collected in Texas were highly virulent when inoculated into guinea pigs and presumptively identified *R. rickettsii* (6). However, more recent attempts to associate *A. americanum* as a potential vector of *R. rickettsii* have been unsuccessful. Burgdorfer et al. (22) failed to identify *R. rickettsii* among 1700 lone star ticks collected in Arkansas, South Carolina, and Tennessee, including ticks collected at sites where RMSF was endemic, although they did identify a high prevalence of a rickettsiae they designated as the WB-8-2 agent (Table 1). Similarly, Goddard & Norment (59) tested 3067 adult *A. americanum* collected from Mississippi, Kentucky, Oklahoma, and Texas between 1983 and 1984. Although a variety of tests yielded evidence of infection by different SFGR, no ticks were found infected with *R. rickettsii* (Table 1). Definitive contemporary evidence incriminating *A. americanum* in the epidemiology of RMSF is lacking, and if natural infection with *R. rickettsii* occurs in this species, it is likely at a low prevalence.

### Other Spotted Fever Group Rickettsiae

Several SFGR have been isolated from *A. americanum* collected in various regions of the United States (Table 1), although whether these various agents cause human disease requires more investigation. Some of these SFGR, such as *Rickettsia parkeri*, are known to cause mild illness when inoculated into guinea pigs (112), and others [isolate 85-1034 ("*R. amblyommii*") possess specific antigens that are

recognized by convalescent-phase serum obtained from humans recovering from illnesses temporally associated with tick bite (33). SFGR transmitted by *A. americanum* will eventually be isolated from sick humans, as has been reported in the past (5). Attack rates of illnesses of presumed tick origin yet of unproven etiology can be substantial in settings in which lone star ticks are the principal or only tick vector present (92).

### *Coxiella burnetii*

*Coxiella burnetii* has been isolated or identified from many species of ticks around the world (118). *C. burnetii* has been isolated from nymphal and adult *A. americanum* collected in eastern Texas (111) and Mississippi (115). However, the role of ticks in transmission of *C. burnetii* to humans is believed to be minimal and largely confined to maintenance of natural transmission cycles among wildlife.

### “*Borrelia lonestari*”

The occurrence of Lyme borreliosis in the southern United States has been a controversial topic. Although *I. scapularis* ticks and small rodents infected with *B. burgdorferi* can be found in southern states (104), naturally occurring human infection has never been demonstrated through isolation of the spirochete. However, beginning in the 1980s, an illness accompanied by a rash resembling erythema migrans (sometimes referred to as southern tick-associated rash illness or Masters' disease) was reported with increasing frequency among patients from Missouri (90), North Carolina (73, 79), and Maryland (9). The tick incriminated in these disease occurrences was *A. americanum*; although in experimental settings, it has not been demonstrated to act as a competent vector for *B. burgdorferi* (105). It is now known that *A. americanum* harbors a spirochete distinct from *B. burgdorferi*, provisionally named “*Borrelia lonestari*,” that has not yet been cultivated (12). The DNA of *B. lonestari* has been identified from a skin biopsy obtained from an erythematous lesion where an attached *A. americanum* was present on a patient (70). Although the public health significance of *B. lonestari* is currently under investigation, it appears likely that this species is a cause of Lyme-like disease in the southern United States (9).

## AMBLYOMMA AMERICANUM-ASSOCIATED EHRlichIOSES

### Historical Perspectives

Until the mid-1980s, bacteria in the genus *Ehrlichia* were not considered to cause human disease in the United States (92a), and studies of ehrlichioses were relegated predominantly to investigators and clinicians in veterinary sciences. Considerable literature existed on *Ehrlichia canis* and *Anaplasma* (formerly *Ehrlichia*) *phagocytophila* (45) tick-borne bacteria with cosmopolitan distributions causing moderate

to severe febrile disease in dogs and ruminants, respectively. However, in 1986 a clinician viewing the peripheral blood smear of a critically ill man with an unexplained febrile illness noted unusual inclusions in several of the patient's white blood cells. These inclusions were subsequently identified as membrane-bound, tightly packed clusters of bacteria called "morulae," which are a characteristic feature of ehrlichiae. The patient had received multiple tick-bites while visiting northern Arkansas two weeks earlier and had been diagnosed presumptively with RMSF (87). Serologic studies later implicated an *Ehrlichia* species as the cause of this patient's severe disease. Within several years, additional patients were diagnosed with ehrlichiosis in the southeastern and south central United States; although these illnesses were initially ascribed to *E. canis* infection (87), the causative organism was subsequently identified as a new species and named *Ehrlichia chaffeensis* (2, 37). Disease caused by *E. chaffeensis* is most commonly referred to as human monocytic ehrlichiosis (HME).

Within the next 13 years, two additional *Ehrlichia* species were reported as agents of human disease in the United States, namely *Anaplasma phagocytophila* in 1994, the cause of human granulocytic ehrlichiosis (HGE) (11), and *Ehrlichia ewingii* in 1999, a second cause of granulocytic ehrlichiosis in humans (19). Through 2001, approximately 1150 cases of HME and 1220 cases of HGE were reported through national surveillance (26, 93) [Centers for Disease Control and Prevention (CDC), unpublished data]. About 20 cases of ehrlichiosis caused by *E. ewingii* have been identified to date [(19, 107, 108); CDC, unpublished data].

### Evidence for Transmission of *E. chaffeensis* and *E. ewingii* by *A. americanum*

Within a few years of the initial description of human ehrlichiosis in the United States, a geographic pattern of cases emerged that approximated the recognized distribution of *A. americanum*, implicating this tick as a potential vector for *E. chaffeensis* (47). This hypothesis was strengthened when *E. chaffeensis* DNA was amplified from pools of *A. americanum* adults collected from several states where cases of disease had originated (3). Subsequent studies demonstrated experimental transmission of *E. chaffeensis* among white-tailed deer by adult and nymphal lone star ticks (49), and retrospective ecologic and serologic surveys identified temporal and spatial associations between lone star tick infestations and the presence and prevalence of antibodies reactive to *E. chaffeensis* in white-tailed deer populations (82).

DNA of *E. chaffeensis* has been detected in lone star ticks collected in at least 15 states in the southeastern, midwestern, and northeastern United States (3, 67, 85, 131, 147). The prevalence of infection in adult ticks tested individually by use of polymerase chain reaction (PCR) generally varies from about 5% to 15% among specimens collected from areas where the agent is endemic (67, 85, 147); however, these prevalence estimates are subject to variation due to different assays employed by different researchers and the intrinsic variability associated with cross-sectional sampling. Crude minimum infection rates (MIRs) determined from



pools of adult ticks have generally ranged from 1% to 5%; however, this method often underestimates the true level of infection at a particular location (85, 131).

Infections have been reported in both adult male and female ticks. As expected, the prevalence of infection appears to be lower in immature stages of ticks than in adults. A sample composed of 81 pools of nymphal *A. americanum* (representing 2723 individual ticks) collected from Harford County, Maryland, showed an overall MIR of 0.8%: The MIR of adult ticks collected at the same location was 3.5% (132). Failure to detect *E. chaffeensis* in nymphs collected at sites with confirmed infections in adult *A. americanum* has also been described (3).

Little is known about the dynamics of infection of *E. chaffeensis* in *A. americanum* populations; however, the prevalence of infection appears to be spatially and temporally discontinuous. Surveys of ticks collected from nearby sampling sites or among ticks collected at the same site during different years revealed marked variability in infection prevalence. Similarly, infection may not always be evident among ticks at a specific location at a particular time of sampling (130, 147).

More than one species of *Ehrlichia* may be present in the same tick or circulate within the same population of ticks, and this may have consequences to host and vector that remain unexplored. An as-yet-unnamed *Ehrlichia* sp. infecting white-tailed deer has been detected in lone star ticks (85), and the DNA of *E. ewingii* has been amplified from questing adult and nymphal lone star ticks collected in North Carolina and Florida (133, 148a). Transstadial passage of *E. ewingii* within *A. americanum* with subsequent transmission to dogs provides further support for the contention that *A. americanum* is a key tick in the maintenance and transmission of several ehrlichiae pathogenic for humans (8).

The replication, growth, and development cycles of ehrlichiae in *A. americanum* and the exact mechanism(s) by which these bacteria are transmitted to the vertebrate host during feeding are unknown. Detection of ehrlichiae in questing nymphal and adult ticks and successful transmission of the pathogen between deer by nymphal and adult ticks infected during the previous life stage confirm that *E. chaffeensis* is passed transstadially (49). Detection of *E. chaffeensis* in larval *A. americanum* has been described (131); however, there are no other data to suggest that transovarial transmission occurs.

## Reservoir Hosts for *Amblyomma*-Transmitted Ehrlichiae

*E. chaffeensis* and presumably *E. ewingii* are maintained in nature as complex zoonoses, potentially involving a wide variety of vertebrates that can serve as competent reservoirs for the bacteria, as sources of blood for tick vectors, or as both. The ability to infect a broad range of hosts is generally regarded as an important factor in promoting the emergence of a zoonotic pathogen (43), and a parallel argument can be applied to the feeding habits of a vector. The catholic feeding proclivity of *A. americanum* for the blood of a wide range of mammalian and avian species is well documented (13, 62). Considerably less is known about which vertebrates can serve as competent reservoirs for ehrlichiae, although the available data suggest that *E. chaffeensis* may infect a wide host range.

## White-Tailed Deer

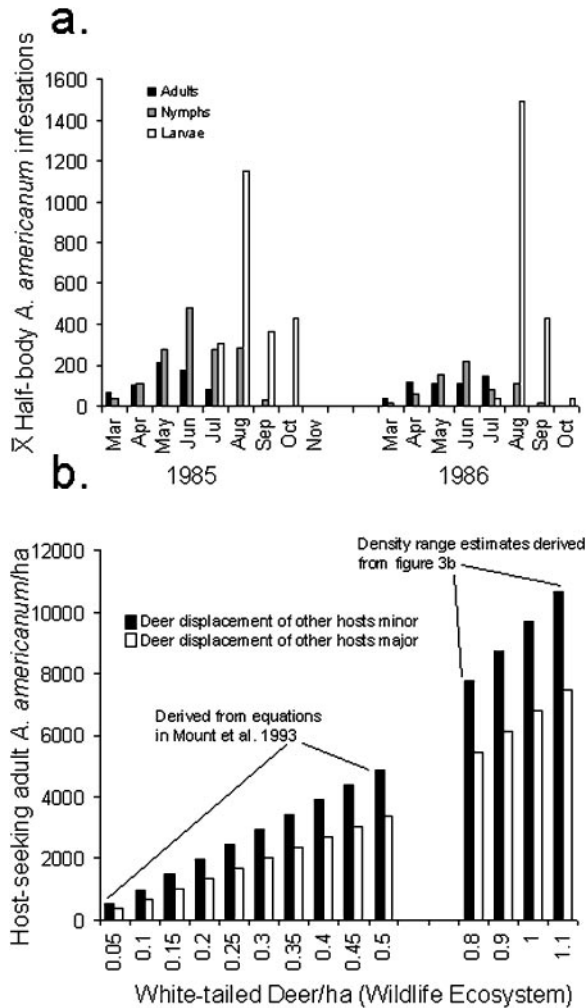
The white-tailed deer (*Odocoileus virginianus*) is the sole vertebrate species currently recognized as a complete and sufficient host for maintaining the transmission cycle of *E. chaffeensis*. White-tailed deer are an important source of blood for adult and immature stages of *A. americanum* (13, 62). Field surveys of white-tailed deer from areas where lone star ticks occur have reported that 80%–100% of sampled animals were infested with all three stages of *A. americanum* ticks; average tick burdens (adults and nymphs) frequently exceed 300 per deer (16, 17). The number of larvae on white-tailed deer has been described as “. . . so numerous that counting was impracticable” in certain circumstances (17). One detailed monthly survey of white-tailed deer in Kentucky and Tennessee reported maximum monthly half-body densities of 1493 larval lone star ticks on deer with corresponding values of 480 nymphal and >200 adult ticks during peak months (15) (Figure 1a). Simulations modeling the density of adult *A. americanum* ticks as a function of white-tailed deer density indicate that this keystone species exerts a profound effect on tick populations (99) (Figure 1b).

White-tailed deer are naturally infected with *E. chaffeensis* in the southeastern United States, as determined on the basis of PCR detection (85) and isolation of the organism (84). In addition, deer experimentally infected with *E. chaffeensis* remain bacteremic for at least 24 days (40) and can infect laboratory-reared larval and nymphal *A. americanum*, which maintain infections transstadially (49).

The prevalence of *E. chaffeensis* infections among populations of white-tailed deer in nature is difficult to determine. Antibody surveys have demonstrated a high prevalence of antibody reactive to *E. chaffeensis* antigens among white-tailed deer populations (frequently >50% of deer at sites where any antibody-positive animals were present) (39, 68, 85, 100), and field data have confirmed a site-specific correlation between antibody prevalence and presence of *A. americanum* (81). However, deer can be infected singly or in combination with several *Ehrlichia* species that are related antigenically to various degrees (41, 80, 148b). Studies using only serologic testing cannot routinely distinguish between antibodies resulting from *E. chaffeensis* infection from those resulting from infection with the antigenically related white-tailed deer agent or *E. ewingii*.

## Other Wildlife

Coyotes serve as hosts for all stages of *A. americanum* (14, 31). In one of the infrequent surveys to quantify tick loads on this canid, coyotes were identified as the relatively most important host of adult *A. americanum* among 13 species of mammals infested with lone star ticks in Oklahoma: 4 of 6 coyotes were infested with 182 adult, 115 nymphal, and 108 larval lone star ticks (75). Coyotes naturally infected with *E. chaffeensis* in Oklahoma have been identified at a high prevalence (15/21; 71%) by use of PCR, suggesting that these animals could be a significant reservoir for *E. chaffeensis* (74a).



**Figure 1** (a) Seasonal activity and abundance of the three life stages of *A. americanum* ticks infesting white-tailed deer in Kentucky and Tennessee, 1985–1986. Figure drawn from data published in (15). (b) Simulated effect of *A. americanum* population density as a function of white-tailed deer density. Figure drawn from equations published in (99). The higher-density estimates were derived from data shown in Figure 3b.

Red foxes (*Vulpes vulpes*) can serve as hosts for all stages of *A. americanum* (139), but counts of *A. americanum* from red foxes are low relative to deer (128). Red foxes were susceptible to infection with a white-tailed deer isolate of *E. chaffeensis* (15B-WTD-GA strain), and ehrlichiae could be reisolated from the blood of experimentally infected animals for 14 days after infection (35). Antibody

reactive to *E. chaffeensis* has been detected in field surveys among both red and gray foxes (35), suggesting that these canids may play a role in the maintenance of *E. chaffeensis*.

Other mammals have been implicated as potential reservoirs for *E. chaffeensis* or antigenically related *Ehrlichia* spp. only through antibody surveys. Raccoons (*Procyon lotor*) are frequently parasitized by all life stages of *A. americanum* (13) and occur throughout much of North America. In addition, raccoons frequently reach their highest population densities in suburban and urban-park locations, so contact rates with humans and domestic pets are high (119). Average lone star tick infestation counts for raccoons ranged between 0 and 1.5 adults, 0 and 80 nymphs, and 0 and 383 larvae per raccoon for surveys conducted in Georgia (116), Kansas (18), Oklahoma (75), North Carolina (107), Tennessee (76, 149), Texas (17), and Virginia (128). However, the results from tick surveys should be interpreted cautiously, considering that the lowest and one of the highest *A. americanum* counts for raccoons came from two sites in different locations of Tennessee (76, 149). Antibody reactive to *E. chaffeensis* antigens was found in 20% ( $N = 411$ ) of raccoons sampled from eight states (30), although PCR failed to amplify the causative species of *Ehrlichia*. A high prevalence of antibodies (20%) was also found among raccoons sampled from an *E. chaffeensis*-enzootic site in Georgia (85).

The Virginia opossum (*Didelphis virginianus*) can serve as a host for all stages of *A. americanum* but does not appear to be a preferred host. Average lone star tick infestation counts for opossums are relatively low and ranged between 0 and 0.2 adults, 0 and 1.7 nymphs, and 0 and 9 larvae per opossum for surveys conducted in Georgia (116), Kansas (18), Oklahoma (75), Tennessee (76, 149), Texas (17), and Virginia (128). Antibodies reactive to *E. chaffeensis* were identified among 8% ( $N = 38$ ) of opossums sampled at an *E. chaffeensis* enzootic site (83).

The role of rodents in the maintenance of *E. chaffeensis* is unknown, although larval and nymphal *A. americanum* parasitize a number of rodent species (17, 62). Antibodies reactive to *E. chaffeensis* at reciprocal titers  $>80$  were identified in 31 of 294 white-footed mice sampled from Connecticut (88); however, the causative agent was not identified. In contrast, no antibodies were detected among 281 rodents of eight species sampled from an *E. chaffeensis* enzootic site in the southern United States (83).

The role of birds as a natural reservoir for *E. chaffeensis* or *E. ewingii* has yet to be defined, although many ground-feeding species serve as important sources of blood for immature stages of *A. americanum* (62). An important example is the wild turkey (*Meleagris gallopavo*); *A. americanum* is called the "turkey tick" in some regions of the midwestern United States because of this close association (42). Average lone star tick infestation counts for turkeys ranged between 15 and 39 nymphs, and 0 and 46 larvae among surveys conducted in Oklahoma (75) and Texas (17), and studies from Kansas also indicate that the wild turkey is an important host for nymphal and larval *A. americanum* (96).

In Russia, ehrlichiae, including an organism identified as *E. chaffeensis*, have been identified by PCR from *I. ricinus* ticks recovered from several species of migratory passerine birds (1). Should it be established that birds do not serve as competent reservoir host for ehrlichiae, their importance as hosts and dispersal agents for ticks potentially infected with these pathogens will not be diminished. As an example, 10 of 46 bird species sampled from a Georgia barrier island were parasitized by nymphal or larval *A. americanum* at prevalences that frequently exceeded 50% from June to August (46).

## Domestic Animals

When serving as a core component in the maintenance cycle of a zoonotic pathogen, perhaps no other animal demands as much public health attention as does the domestic dog. Their popularity as companion animals (>61,500,000 owned dogs in the United States as of March 1999; American Pet Association, <http://www.apapets.com/>) and their access to both tick-infested habitats and to human habitations make them a priority in investigations into the natural history of the human ehrlichioses. Dogs serve as hosts for all stages of *A. americanum* (13, 62) and can serve as a competent reservoir host for *E. chaffeensis* and *E. ewingii* (50).

Ehrlichial infections among dogs are common in many regions of the United States. In southeastern Virginia, 38% of sampled dogs ( $N = 74$ ) had antibody reactive to *E. chaffeensis* antigens, and 8 of 19 had ehrlichial DNA in whole-blood samples tested by a nested PCR (38). A survey conducted in Oklahoma found similar results: 7 of 65 dogs had antibody reactive to *E. chaffeensis* antigens and 4 animals had *E. chaffeensis* DNA in whole-blood samples tested by a nested PCR (101). Caution is warranted when interpreting the results of surveys based solely on serologic testing because dogs may be concurrently infected with multiple species of *Ehrlichia* that are antigenically related (77).

Domestic goats (*Capra hircus*) serve as hosts for all life stages of *A. americanum* (13, 62). Although knowledge of goats as a reservoir species for *E. chaffeensis* in the United States is limited to a single report, a high prevalence of reactive antibody (28/38 animals; 74%) and presence of ehrlichial DNA in whole blood (6/38; 16%), as determined by PCR, suggest a potential reservoir role for this common animal (44). Of special interest was the isolation of *E. chaffeensis* from a single goat sampled at time points 40 days apart, suggesting a persistent bacteremia.

In summary, it appears certain that *E. chaffeensis* has a broad range of vertebrate hosts that can act as competent reservoir hosts for transmission of the bacterium to various stages of the lone star tick. At least three species of mammals in the order Carnivora (all in the family Canidae) and two in the order Artiodactyla (families Bovidae and Cervidae) have been infected by *E. chaffeensis* in natural or experimental settings. The white-tailed deer is a competent reservoir host for *E. chaffeensis* and a critical or even keystone host for *A. americanum*. Little is known about potential reservoirs for *E. ewingii* other than domestic dogs, although it is likely that one or more species of wildlife are involved in the maintenance of this agent.

## EPIDEMIOLOGY OF *AMBLYOMMA*-ASSOCIATED HUMAN EHRLICHIOSES

Although *E. chaffeensis* was the first *Ehrlichia* identified as a human pathogen in the United States, our knowledge of the biology of *A. phagocytophila*, which was isolated several years later, is already more substantial. Epidemiologists and biologists have utilized the public health infrastructure and research findings accumulated over nearly two decades of study of Lyme borreliosis and *I. scapularis* in the northeastern and northcentral United States toward understanding the epidemiology of HGE.

In contrast to cases of HGE, most cases of HME and all cases of *E. ewingii* ehrlichiosis (EWE) have been reported from the southcentral and southeastern United States (53, 93, 108), where *A. americanum* reaches its greatest population densities (Figure 2a). Mandated national surveillance and reporting of the ehrlichioses has been in effect only since 1999. Although reporting by individual states has been incomplete, these data indicate a region of highest risk ranging from central Texas through Oklahoma and Missouri east to Virginia and all states to the south (Figure 2b). Cases of HME are reported sporadically along the East Coast, most notably on the Atlantic coastal plain. DNA from *E. chaffeensis* has been recovered from *A. americanum* from as far north as Connecticut and Rhode Island (Figure 2a). Many human cases of ehrlichiosis are diagnosed by serologic testing, and antibodies resulting from infection with *E. ewingii* or *A. phagocytophila* can cross-react with *E. chaffeensis* antigen (19). In addition, the travel histories of persons suspected of having ehrlichiosis are usually not provided when serum samples are submitted for diagnostic evaluation to reference laboratories, such as CDC, so that some cases of ehrlichiosis relegated to a specific state in summary reports may have been imported (93). Finally, lone star ticks can be accidentally transported to or may exist in foci within states not considered within the range of *A. americanum* (Figure 2a). An analysis based on tick specimens parasitizing humans accessioned into the U.S. National Tick Collection identified lone star ticks attached to persons from Michigan, Nebraska, New Mexico, Wisconsin, and Wyoming (95).

Although *E. chaffeensis* has been isolated only from the United States and EWE is only documented from this country, there are data indicating that human infections with antigenically related ehrlichiae occur in Europe (102), Asia (63), South America (120), and Africa (142). Because the only proven tick vector of *E. chaffeensis* (i.e., *A. americanum*) is restricted to the New World, these findings suggest involvement of other tick species in the transmission of HME, the cosmopolitan distribution of ehrlichiae antigenically related to *E. chaffeensis*, or both. Ehrlichiae that are closely related or identical to *E. chaffeensis* have been identified from a variety of ticks collected in Asia (1, 127), although the significance of these findings for human disease is unclear.

Reliable incidence data on the *Amblyomma*-transmitted ehrlichioses derived from active, population-based surveillance are restricted to a few localities and do

not exist for EWE. The estimated incidence for hospitalized cases of HME was 5.5 per 100,000 persons in southeastern Georgia, which was higher than that for RMSF during the same period (54). Estimates of 8 and 14 cases of HME per 100,000 persons during 1997 and 1998, respectively, were obtained by active surveillance for HME in southeast Missouri (103). The frequencies of occurrence of HME in cohorts of patients presenting with fever and a history of tick bite in Tennessee (7/38 patients) (129a) and central North Carolina (10/35) were nearly identical (24) and similar to the number of RMSF diagnoses. From these observations we conclude that where endemic, HME occurs at an incidence similar to that of RMSF, a well-known tick-borne disease considered uncommon but not rare.

HME is a highly seasonal disease. Although cases have been reported during March through November, about 70% of cases occur during May through July (53, 129). This seasonality corresponds to the peak feeding-activity periods of nymphal and adult *A. americanum* throughout much of their range (Figure 1a). Reports of HME into the late fall and winter are unusual but may be more common in the South (117).

HME is predominantly a disease of adults; most patients are >40 years of age, and in all age groups men are diagnosed with the disease more frequently than women (53). Of particular note is that HME in children is relatively rare: Among the first 250 reported cases of ehrlichiosis, <10% were in individuals 2 to 13 years of age (53). The reasons for this age distribution remain unclear, although the severity of HME correlates with immune function, which becomes increasingly impaired with age.

Most HME cases occur as sporadic infections. Recreational or occupational activities that place individuals in tick-infested habitats are well-documented risk factors for infection. A recollection of recent tick bite was reported by 68% of ehrlichiosis cases in a national survey (53), but that figure can exceed 80% in specific investigations (103, 129). Rare outbreaks of HME have occurred among golfers living in a retirement community in Tennessee (129) and among military personnel participating in field training exercises (92).

Because lone star ticks transmit several bacterial pathogens, coinfections may occur. In North Carolina, a concurrent infection with *E. chaffeensis* and SFGR has been diagnosed (126), and several seroepidemiologic studies have demonstrated simultaneous seroconversions to *E. chaffeensis* and SFGR among military personnel exposed to *A. americanum*-infested habitats (92).

## FACTORS IN THE EMERGENCE OF *AMBLIOMMA*-ASSOCIATED EHRLICHIOSES

### Recent Clinical Recognition or New Diseases?

It is likely that the observation of morulae in white blood cells of a patient with an unexplained febrile illness was noted long before the formal discovery of

ehrlichiosis in 1986. Peripheral blood smear evaluation was the standard of hematologic evaluation before widespread availability of automated cytometry, and morulae would have probably been noted, but their connection to an ehrlichia was either missed or left uninvestigated. In 2002, even experienced medical technologists have trouble differentiating true morulae from intraleukocytic inclusions associated with unrelated infectious or noninfectious conditions.

Is there something unique about the clinical presentation of the ehrlichioses that would have made these diseases stand out and led to their recognition as distinct and novel human diseases? In fact, the early disease manifestations of HME and EWE are relatively nonspecific and present a diagnostic challenge even to physicians knowledgeable about tick-borne diseases (143). As disease progresses, involvement of multiple organ systems may complicate the clinical course and result in various life-threatening scenarios. However, the clinical course is often nondescript when complicating underlying factors, such as immunosuppression, are lacking (108), suggesting that the ehrlichioses, had they been occurring at appreciably lower incidence than at the present time, would have been difficult to identify as unique disease entities. The protean clinical presentations range from generalized and relatively vague initial symptoms to more targeted complaints, and initial diagnoses have included "viral syndrome," upper respiratory infection, pneumonia, meningoencephalitis, cholecystitis, pharyngitis, urinary tract infection, epididymitis, or prostatitis (48, 108, 109). Even the hematologic abnormalities associated with HME (e.g., leukopenia and thrombocytopenia) are consistent with alternative diagnoses, such as sepsis, thrombotic thrombocytopenic purpura, or hematologic neoplasia (69, 89). The broad differential, coupled to a low incidence of disease, would have made the ehrlichioses difficult to identify until a certain threshold frequency of human disease was crossed. Although the *Amblyomma*-associated ehrlichioses undoubtedly occurred in the past, we believe that factors affecting the incidence and distribution of HME and EWE have made it increasingly likely that these diseases would be documented.

## The Concept of Emerging Disease

The term "emerging infection" has been overused; however, the designation as originally intended (i.e., to signify new diseases or preexisting diseases that are rapidly increasing in incidence) still has relevance. Although changes in public health surveillance practices and the availability of diagnostic assays play a major role in determining disease incidence, there are also a number of factors independent of human activities that can radically influence the emergence of a zoonotic disease (Table 2). Zoonoses are diseases of animals that are transmissible to humans, and the epidemiology of vector-borne zoonoses must be understood within the context of natural maintenance cycles of pathogens that involve wildlife and arthropods. Understanding the natural history of zoonotic agents is no academic luxury because effective control of the human diseases caused by these pathogens frequently hinges on targeting the vector or reservoir populations. In addition, human disease is an insensitive indicator of the magnitude of the zoonotic-pathogen reservoir and



**TABLE 2** Factors in the emergence of *Amblyomma*-associated zoonoses with emphasis on the ehrlichioses

Factor in emergence	Example	Reference
Vector dynamics	Increase in <i>A. americanum</i> population density	(56)
	Increase in geographic distribution of <i>A. americanum</i>	(71, 94)
Reservoir host dynamics	Increase in population density and geographic distribution of vertebrate host populations (especially white-tailed deer, turkeys) that serve as hosts for <i>A. americanum</i>	(91, 94)
	Increase in competent reservoir host (e.g., white-tailed deer) populations for <i>E. chaffeensis</i> and <i>E. ewingii</i>	(91, 137, 148b)
Human behavior	Increased human contact with natural foci of infection through recreation or occupation	(109, 129)
	Improved surveillance and reporting	(93)
	Habitat modification and climate change	(60, 106)
Human demographics	Increasing size of human population >40 years of age	(140)
	Increasing size and longevity of immunocompromised populations	(25, 110, 122)
	Population shift to rural environments	(86, 122)

the dynamics of transmission in nature cycles. These aspects of the maintenance cycle are usually “silent” and cannot be appreciated without special study.

Several recent reviews have examined factors relevant to the emergence of infectious diseases among wildlife (34, 43) and vector-borne diseases of humans (144). We focus our discussion on the various factors influencing the maintenance of ehrlichial pathogens in nature and consider how dynamic changes in these factors could drive emergence by affecting the frequency and severity of the corresponding human diseases and the geographic region affected by endemic disease. We first consider the complex interactions of tick vectors and vertebrate hosts that are sensitive to environmental influences that can drive epizootics. The emergence and spread of Lyme disease in the eastern United States is a classic example of how changes in environmental conditions have influenced patterns in vertebrate-host and vector-tick distribution and population densities to affect the incidence of a human disease (137). In addition, changes in the patterns of susceptibility within a population can be a critical factor in disease emergence, both in increasing the opportunity for sporadic transmission of pathogens to humans (98) and in the dynamics of epizootics occurring among wildlife populations (43).

### Dynamics of Reservoir Host and *A. americanum* Populations

The greatest influence on the emergence of *Amblyomma*-associated ehrlichioses has been the explosive growth of white-tailed deer populations in the United States. Lone star ticks were identified as the most common species of tick (73.3% of 367

attached ticks) parasitizing humans in a survey of tick attachment sites on humans conducted in Georgia and South Carolina from 1995 to 1998 (51). However, a similar study conducted in South Carolina during 1973–1974 found that *A. americanum* contributed only 7.7% ( $N = 220$ ) of the sample of human-biting ticks (21). Increases in white-tailed deer populations have been suggested as a primary factor in driving this increase in lone star tick abundance (52).

The dramatic rise in white-tailed deer numbers was preceded by the reforestation of extensive tracks of land originally abandoned by westward-bound emigrants in the early 1800s (91). Recovery of deer populations was not an inevitable or monotonic process, and a period of intense overharvesting kept populations at historic lows until the early 1900s, when most deer herds in the southeastern United States reached their nadir (Figure 3a). From these historic lows, the number of white-tailed deer increased about 50-fold during the twentieth century, from an estimated 350,000 animals in 1900 to at least 17 million animals by the mid-1990s (91). This remarkable increase in population has been matched by an equally impressive range expansion throughout most suitable habitats in the eastern half of the United States (Figure 3b) (Quality Deer Management Association, Watkinsville, Georgia, <http://www.qdma.com/>). Similar links between white-tailed deer and increases in the number and range of *I. scapularis* and the emergence of Lyme disease, babesiosis, and HGE have been described (137).

Deer were nearly extirpated from northeastern states until the reintroduction efforts of the 1930s (121). In the southeastern United States, where this mammal is closely linked to increases in the abundance and expanded geographic range of the lone star tick (52, 99), similar decline and resurgence occurred. As an example, by 1920 native deer were considered extirpated from nearly all of western Virginia, and in the Tidewater area remnant deer herds remained only in remote areas inaccessible to humans (74). An intensive campaign of white-tailed deer restoration resulted in repopulation of most of the state by 1970 (74). The deer population of the southern United States achieved its current level and distribution only within the past few decades, and population numbers have continued to increase as assessed by white-tailed deer harvest numbers (123) and counts of deer-vehicle collisions (91). The impact of white-tailed deer on the dynamics of lone star tick populations has been discussed (see also Figure 1b).

Other important vertebrate hosts for *A. americanum* and potential reservoirs for *E. chaffeensis* and possibly *E. ewingii* have undergone similarly impressive increases in population growth and geographic distribution. Coyotes have expanded their range throughout North America since the 1800s, a time when they were restricted to the Great Plains and the western United States (97). In the southeastern United States, the number of coyotes has increased dramatically, as evidenced by an increase in harvest of these animals in Mississippi from 500 in 1975 to 40,000 in 1988 (97). These carnivores exist in most habitats and have become established in suburban and urban locations where contacts and attacks on humans and domestic animals are increasingly reported (10). These developments increase the potential for infected lone star ticks to be seeded into the peri-domestic environment.

Other nonmammalian vertebrates that are considered important sources of blood for lone star ticks but whose competence as reservoirs for ehrlichiae is unknown have also experienced increases in geographic range and population numbers. For example, the dynamical change in geographic distribution and abundance of the wild turkey paralleled that described for white-tailed deer. By the early to mid-1800s, populations were extirpated from New England, and by 1920 only 21 of the original 39 states with turkeys had remaining populations (72). Between 1959 and 1990, estimates of the turkey population of the United States increased from 500,000 to 3.5 million (72), and as determined by the basis of hunter kills, population numbers continue to increase at a high rate (94).

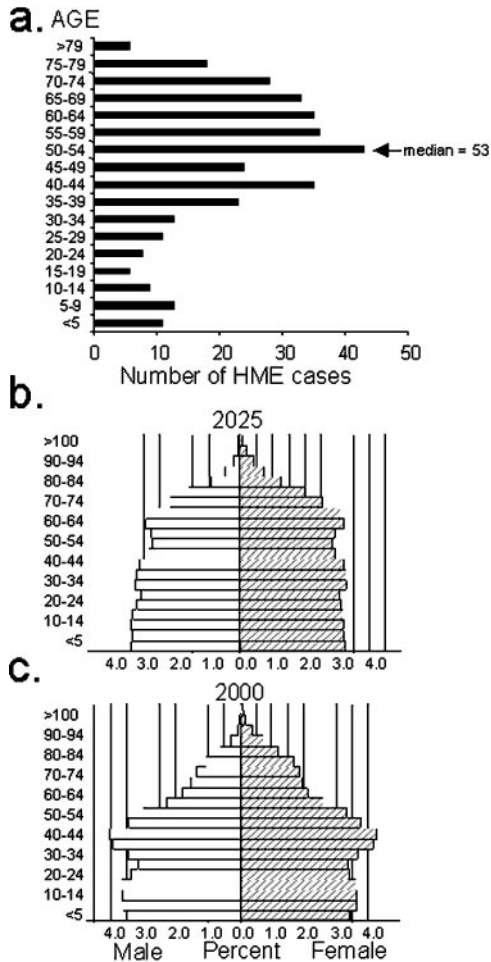
As wild turkey populations have increased throughout their historic geographic range, they are credited with reintroducing and increasing population densities of the lone star tick. Concurrent expansion and increases in turkey and lone star tick populations have been reported at the extremes of their known range in New York to the north (94) and Kansas to the west (Figure 2a) (96). Restoration programs have introduced turkeys into every state except Alaska, including 10 states considered outside of the ancestral range of this bird (72). It appears certain that the geographic range of *A. americanum* will continue to expand with the success of this host. It is also likely that in some of these newly colonized locations, infections in humans with tick-transmitted ehrlichiae will occur.

## Improved Diagnostics and Surveillance

The development and increasing availability of diagnostic reagents, changes in surveillance activities, and requirements for national notification have had a major impact on our understanding of the epidemiology and emergence of HME (27). The number of cases of ehrlichiosis reported to state health departments and to CDC increased from 69 in 1994 to 363 in 2000 [(93); CDC, unpublished data]. However, diagnostic tests based on serology alone are not sensitive indicators of disease early in the clinical course (28), and reporting remains inconsistent or nonexistent in several southern states where HME and EWE are of special concern. Enhanced surveillance and education programs are required to raise the level of diagnostic suspicion for HME and EWE in order to provide details as to the full spectrum of disease, and this will undoubtedly lead to a better appreciation for the public health impact of HME and elucidation of the epidemiology of EWE.

## Expansion of Highly Susceptible Human Subpopulations

One fundamental factor contributing to the emergence of new pathogens and diseases has been change in host susceptibility, operating at the population level through immunosuppression. The various means by which large segments of the human population may become immunosuppressed include aging, malignancy, and infectious causes (98). Demographics indicate that the U.S. population is becoming increasingly weighted toward the older age groups, and the ehrlichioses



**Figure 4** (a) Human monocytic ehrlichiosis (HME) is predominantly a disease of adults and the elderly (CDC, previously unpublished data). (b) Estimated changes in the population structure of the United States between 2025 and (c) 2000 Data from (141).

appear to be predominantly diseases of adults and especially severe in the elderly (Figure 4a). In one of the first epidemiologic investigations of 149 patients with HME, increasing age (>60 years) and delay (>8 days) in effective antibiotic treatment were the only independent risk factors for severe or fatal illness (53). Aging and the associated “immunosenescence” of the immune system are a well-described but imperfectly understood phenomenon (114). The United States Census estimates that the percentage of the population >45 years of age will increase from 34.9% in 2000 to 41.3% in 2025 (Figure 4b,c) (141). Coupled with

longer life expectancy is better general health, which encourages many older persons to enjoy outdoor activities that bring them into contact with ticks (129). This combination of factors indicates that the number and severity, if not the overall incidence, of HME and EWE cases will increase as the size of the most susceptible sector of the population expands to unprecedented levels.

Because ehrlichiae are obligately intracellular pathogens, it is likely that intact humoral and cell-mediated immunity are essential for successful clearance of *E. chaffeensis*. Severe and fatal HME have been described repeatedly in persons with compromised immunity from human immunodeficiency virus (HIV) disease (108) and immunosuppressive therapies (7, 124). Although the absolute prevalence of HIV among persons in nonmetropolitan areas remains significantly lower than in urban centers, the number of HIV-infected persons residing in nonmetropolitan areas has increased most rapidly since the 1980s (55). The expansion of HIV into rural populations is particularly evident in the southeastern United States (29), where the risk of HME and EWE is greatest (93). New therapies for HIV have braked the progression of HIV infection in many patients, permitting a level of health that allows occupational and recreational activities not previously possible. Many of these activities (e.g., hunting, hiking, camping, or working outdoors) place these patients at increased risk for tick bites and have been directly linked with acquisition of *E. chaffeensis* in HIV-infected persons (108).

Other noninfectious causes of immunosuppression have also been identified as increasing the risk of ehrlichiosis and the potential for severe disease. The number of persons living with transplants and receiving potent immunosuppressive drugs will approach 200,000 by the end of 2002 (United Network for Organ Sharing, <http://www.unos.org/framede??fault.asp>). Given the relatively small number of transplant recipients, it is even more remarkable that HME and EWE have been diagnosed in transplant patients (19, 124).

## Technology, Land Use, and Human Activities

Many factors contributing to the increasing size of the segment of our population most susceptible to infectious diseases, such as HME and EWE, are the direct result of technological advances in medicine, pharmacology, and public health practice. Important examples already discussed include improvements to general health (e.g., through better nutrition and childhood immunizations) that have led to greater longevity and the aging of the U.S. population and increases in the number of persons on potent immunosuppressive drugs as part of medical therapy (98).

The reforestation of the eastern United States and the emergence of zoonotic pathogens associated with white-tailed deer and the ticks that feed on deer have been discussed. However, the effect of these factors was magnified by a dramatic reversal of a demographic trend in the United States that first became noticeable in the twentieth decennial census conducted in 1980. In contrast to historical and global trends, the U.S. population between 1970 and 1980 grew faster in nonmetropolitan regions (17.1%) than in metropolitan regions (10.0%), with much of the growth

occurring in true rural environments rather than suburbia (86). From 1990 to 1999, the growth rate of nonmetropolitan areas, although still substantial, had slowed to 7%, whereas metropolitan areas grew by 10% (141). The convergence of population growth in rural environments, the increase in the numbers and geographic distribution of tick vectors and reservoir hosts, and the increase in the proportion of the population considered to be highly prone to more severe disease helped drive the emergence of *Amblyomma*-associated zoonoses.

The local species diversity available to a pathogen can play a role in either promoting or hindering its persistence and rate of geographic spread (135). The impact of humans in altering the components of ecological communities has been dramatic. For example, humans have reduced the numbers of large predators, such as wolves (*Canis lupus*) and mountain lions (*Felis concolor*), throughout North America. Removing predators from predator-prey cycles can have effects beyond the direct effects on competitors and prey populations. The geographic spread and increase in population densities of white-tailed deer and the white-footed mouse (*Peromyscus leucopus*) have been facilitated by removal of predators, and this diminished biodiversity may have contributed to the rapid emergence of a human disease in the case of Lyme borreliosis (106).

Recreational opportunities associated with rural or suburban living frequently have been implicated as risk factors for acquiring tick-borne diseases. In 1947, Topping (138) identified golf as a potential risk factor for RMSF and postulated that the incidence of the disease would be greatest among less skilled golfers, who would spend more time in the rough. Nearly 50 years later, Standert et al. (129) demonstrated just such an association when an outbreak of HME occurred in a retirement golf community in Tennessee. Golfers with average scores > 100 had 2.4-fold-greater odds of having antibody to *E. chaffeensis* than those with scores < 100 (129). In addition, individuals with a habit of retrieving a lost ball had 3.7-fold-greater odds of having antibody to *E. chaffeensis* than those golfers who simply used a new ball. Between 1970 and 2000, the number of persons playing golf in the United States more than doubled from about 11 million to almost 27 million, and the number of golf courses increased from 10,848 to 17,108; approximately 27% of golfers are age 50 or over (National Golf Association, <http://www.ngf.org/faq/#1/>).

## CONCLUSIONS AND FUTURE PROSPECTS

During the next 25 years, the number of cases of disease caused by *A. americanum*-associated pathogens will likely continue to increase, partly because of biologic factors that influence the likelihood of susceptible humans coming into contact with infected lone star ticks and partly because of increasing physician awareness and our ability to diagnose these diseases. However, the many biological, sociological, and environmental factors that drive the distribution and intensity of transmission of zoonotic pathogens are not static, and certainly other wildcards exist that may change projections of the frequency of illness in the human population. One such

factor is the contentious issue of climate change and its potential effect on vector-borne diseases. The ecology of arthropod vectors and their hosts and the resulting transmission dynamics of the pathogens they transmit are strongly influenced by climatic factors (60). Although the impact of climate change on the ehrlichioses is unknown, models suggest that another tick-borne disease, RMSF, which has an incidence similar to HME, may decline if average summertime temperatures increase in the southeastern United States, reducing survival of *D. variabilis* ticks (61). From a medical entomologic perspective, the impact of *A. americanum* on human health has changed dramatically in a relatively short span of time since 1986. Revisiting this topic in future years should be informative and instructive.

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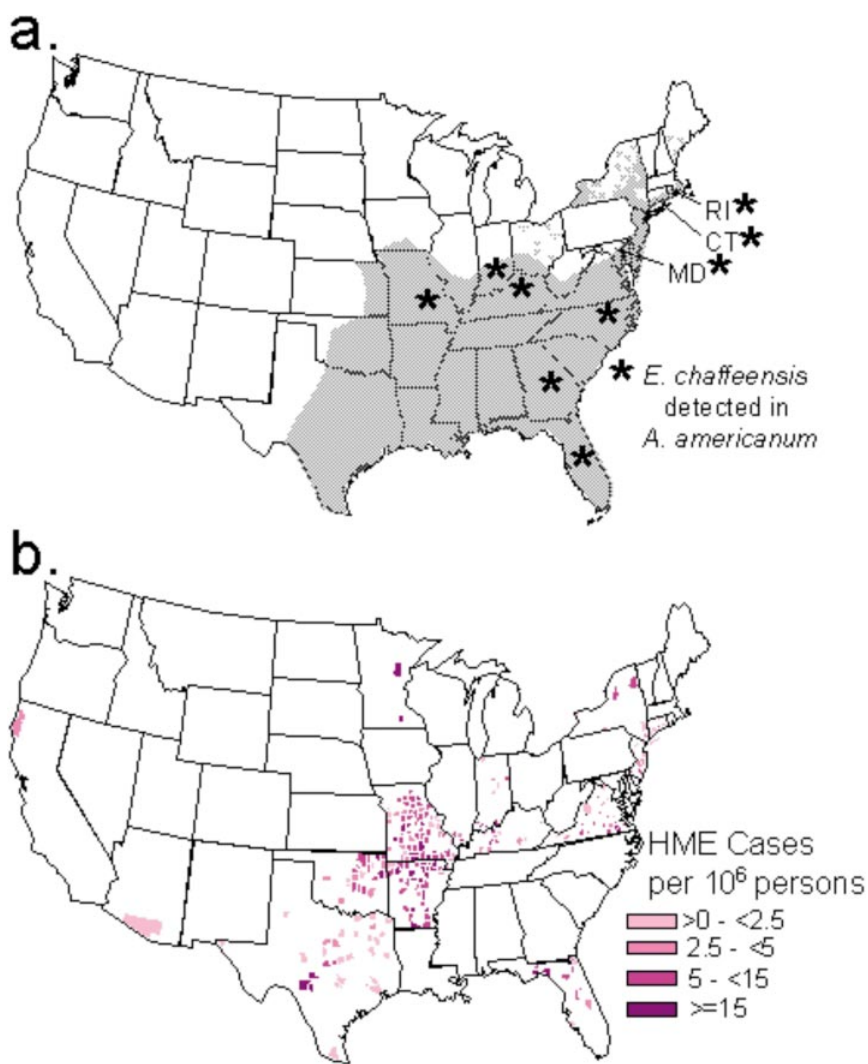
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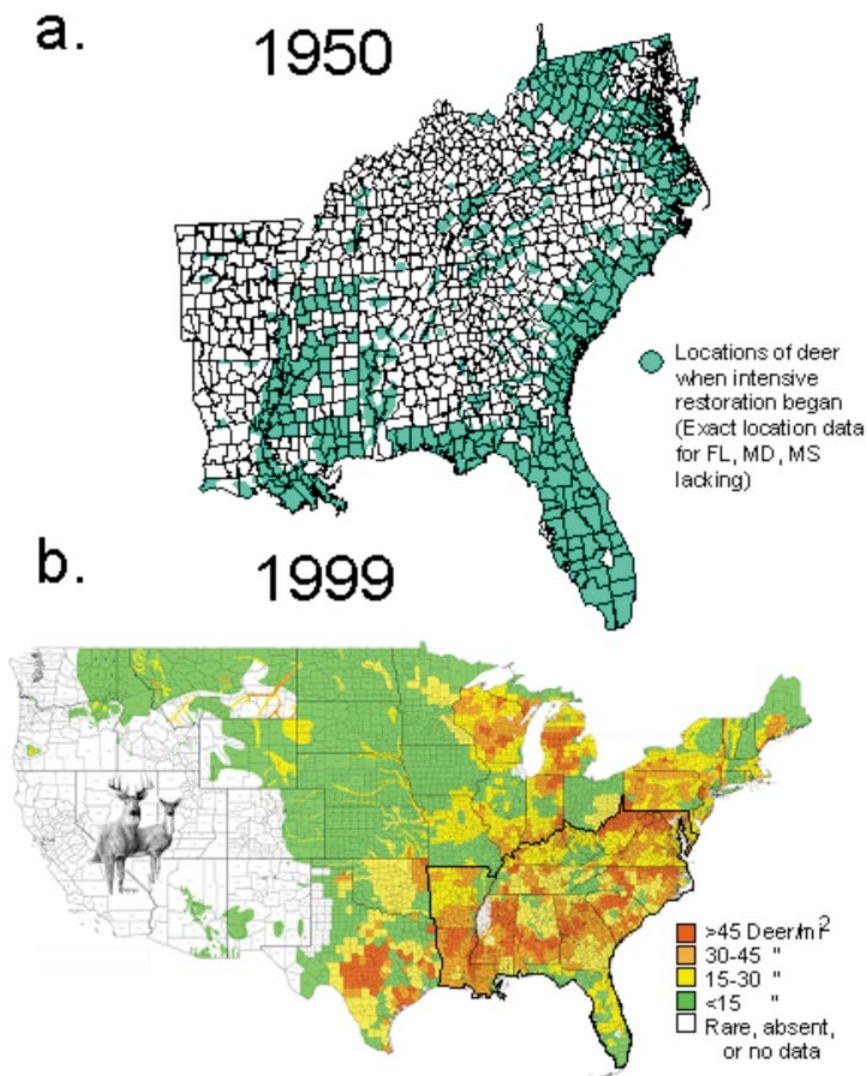
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**Figure 2** (a) Approximate distribution of *A. americanum* based on published data or maps (13, 71, 94). (b) Average annual incidence of HME, 1998–2000, based on states reporting data to the level of county (ehrlichiosis is not notifiable in all states where *E. chaffeensis* and *E. ewingii* are endemic) (26, 93).





**Figure 3** (a) Estimated distribution of extant deer populations in the southeastern United States circa 1950. Map was redrawn from maps produced by the Southeastern Cooperative Wildlife Disease Study (SCWDS), Athens, Georgia, from data compiled by State Game and Fish Biologists of the Southeastern Region. Maps may differ from previously published maps (74) due to problems in resolution. (b) Estimated white-tailed deer density, 1999. Map provided and published with permission of Quality Deer Management Association, Watkinsville, Georgia, 30677 (<http://www.qdma.com/>).

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