ARTICLE

Ehrlichia chaffeensis Seroprevalence Among Children in the Southeast and South-Central Regions of the United States

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Background: The reported annual incidence of human monocytic ehrlichiosis, which is due to infection with *Ehrlichia chaffeensis*, is as high as 5.5 per million in some states, but serosurveys suggest much higher infection rates in some populations.

Objective: To estimate the prevalence of *E chaffeensis* infection among children aged 1 to 17 years living in the southeast and south-central United States.

Design: Cross-sectional serosurvey.

Setting: Seven academic pediatric medical centers in the southeastern and south-central United States.

Patients: Nineteen hundred ninety-nine children (approximately 300 at each center) having their blood drawn for any reason.

Main Outcome Measure: The presence of antibody at 2 different cutoff titers to *E chaffeensis*, as detected by indirect immunofluorescence assay.

Results: Overall, 250 children (13%) had *E chaffeensis* antibody titers of 1:80 or higher and 61 (3%) had titers of 1:160 or higher. Age-adjusted seroprevalence rates varied widely between sites. At 1:80 or higher, the highest rate was in Winston-Salem, NC (22%), and the lowest was in Louisville, Ky (2%). At 1:160 or higher, the highest rate was in Kansas City, Mo (9%), and the lowest was in Oklahoma City, Okla (<1%). In univariate analyses, no associations were found between seroprevalence at either cutoff value and sex, race, source of specimen, or residence demographics. However, age was a significant predictor of seroprevalence at both cutoff values. In multiple logistic regression analysis, study site and age remained strong predictors of seroprevalence, but living in a nonurban ZIP code was not significantly related.

Conclusion: Infection with *E chaffeensis*, or related ehrlichiae, may be more common in children than previously recognized.

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EHRLICHIAE ARE small, gram-negative, obligate intracellular coccobacilli belonging to the family Rickettsiaceae. They infect circulating leukocytes, where they divide into host membrane-bound clusters called morulae, which are visible by light microscopy.[1,2] The first case of human ehrlichiosis in the United States was reported in 1987 in a man who had received a tick bite in Arkansas.[3] Initially thought to be due to *Ehrlichia canis*, an established pathogen in dogs,[4] this infection was subsequently shown to be caused by a closely related species, now known as *Ehrlichia chaffeensis*.[5,6] This agent is the cause of human monocytic ehrlichiosis, which is distinguished by a predominance of morulae in mononuclear cells. *Amblyomma americanum* and *Dermacentor variabilis* have been suggested as vectors, and deer are likely reservoirs.[7]

Descriptions of clinical illness, which are biased toward more severe manifestations of disease, emphasize the occurrence of fever, headache, myalgia, leukopenia, thrombocytopenia, anemia, and the elevation of hepatic transaminase levels; rash is seen less commonly than in those with Rocky Mountain spotted fever.[8,9] The median duration of illness is about 3 weeks, and the fatality rate is as high as 5%. Whereas most reported disease is in older adults,[8,9] ehrlichiosis has been reported in children,[10,11] with recent reports[12] emphasizing the occurrence of severe life-threatening disease. Ehrlichiosis is almost certainly underrecognized. The highest reported average annual statewide incidence rate for human monocytic ehrlichiosis is only 5.5 cases per million (Arkansas).[13] Despite reporting rates of this magnitude, several studies show ehrlichiosis to be a relatively common cause of undifferentiated febrile ill-

PATIENTS AND METHODS

POPULATION SPECIFICATION AND SAMPLING

Seven sites located in the "tick belt" of the southeastern and south-central United States participated in the study. From east to west, these sites were as follows: Winston-Salem, NC; Louisville, Ky; Nashville, Tenn; Memphis, Tenn; Little Rock, Ark; Kansas City, Mo; and Oklahoma City, Okla. Approximately 300 patients aged 1 to 17 years were studied at each site. Plasma or serum specimens were obtained from residual volumes in the site's chemistry laboratory after the appropriate clinical tests were performed. This method thus sampled children with any diagnosis having blood drawn for any reason. Because specimens were stripped of unique personal identifiers and were anonymously coded, the need to obtain informed consent was waived by each institution's human studies committee. Collections occurred between February 22, 1998, and July 24, 1998, at all sites except Oklahoma City, where collections occurred between July 21, 1999, and September 27, 1999. Patient data recorded for each specimen included the following: study site, date of birth, date of specimen collection, source of specimen (hospital admission, emergency department visit, or other outpatient visit), sex, race, and ZIP code of residence.

SEROLOGICAL TESTS

Specimens were tested in one laboratory (PanBio InDx, Inc, Baltimore, Md) for antibodies to *E chaffeensis* by indirect immunofluorescence assay (IFA). Vero cells infected with strain 91HE17[23] were fixed onto glass slides containing 6-mm wells. Serum samples were diluted 1:80 in phosphate-buffered saline and reacted with antigen wells at room temperature for 30 minutes. Slides were then washed with phosphate-buffered saline, rinsed with deionized water, and air dried. Bound antibodies were detected using a fluorescein isothiocyanate–conjugated polyclonal goat antiserum (diluted 1:100 in phosphate-buffered saline) reactive with human IgG, IgA, and IgM (American Qualex, San Clemente, Calif). After 30 minutes at room temperature, slides were rinsed with phosphate-buffered saline and counterstained with eriochrome black. Blinded laboratory personnel examined the slides for bright yellow bodies corresponding to intracytoplasmic morulae using epifluorescence microscopy. Specimens that were positive for morulae at the screening dilution of 1:80 were retested and diluted to determine the end point titer. All positive serum samples were also tested for antibody to *R rickettsii* and *Rickettsia typhi* (Rickettsia IFA IgG Test Kit [used according to the manufacturer's instructions]; MRL Diagnostics, Cypress, Calif). Each assay included positive and negative controls. To control for storage and handling, and to provide an assessment of signal detection, 6 control serum samples were sent to 6 of the sites for random inclusion in their sequence of specimens (control serum samples were not available for Kansas City). Two of these were positive for *E chaffeensis* antibody, 2 were positive for *R rickettsii* antibody, and 2 were negative for antibodies to both organisms.

ANALYSIS

Data were stored and analyzed on a computer (Macintosh PowerBook G3; Apple Computer, Inc) running a statistical analysis program (StatView 5.0; SAS Institute Inc, Cary, NC). The 1998 Centers for Disease Control and Prevention surveillance definition of probable ehrlichiosis[24] included an IFA antibody titer of 1:64 or higher (the 2000 definition refers only to cutoff values established by individual laboratories[25]). However, cutoff values for positive IFA titers in published seroprevalence studies[16-18,22] of ehrlichiosis vary from 1:64 or higher to 1:80 or higher. Because standards for interpretation of these assays in seroepidemiologic studies do not exist, the present data were analyzed at a cutoff value of 1:80 or higher and at a more stringent cutoff value of 1:160 or higher. For analysis, age was collapsed into the following categories: 1 to 6, 7 to 12, and 13 to 17 years. Race was dichotomized into white and nonwhite. Based on 1990 census data, ZIP codes were demographically categorized as follows: (1) urban (≥75% of households classified as urban [places of ≥2500 persons incorporated as cities, villages, boroughs, and towns] or urbanized (places and their adjacent densely settled surrounding territories [at least 1000 persons per 2.6 km^2] that together have a minimum of 50 000 persons); and (2) all others.[26] Categorical associations between variables were sought in univariate analyses using the χ^2 test; in all cases, expected cell frequencies were greater than 5. Site-specific seroprevalence rates were adjusted for differences in age distribution using the entire study population as the reference. Multiple logistic regression was performed using 6 variables: study site, age, source of specimen, residence, race, and sex. Variables that were highly significant in univariate analyses were entered into the model first, and for each variable, the element with the lowest seroprevalence rate was used as the reference level. Significance for all analyses was defined at an α level of .05.

ness in adults, with[14] and without[15] a history of a tick bite. The occurrence of subclinical ehrlichiosis was underscored in a study[16] of a golf-oriented retirement community in eastern Tennessee, which demonstrated serological evidence of prior infection in 12.5% of residents, although few reported compatible illnesses. Similarly, 4.6% of residents of a semirural subdivision in northern California had antibodies to *E chaffeensis* but no recollection of illness suggesting ehrlichiosis.[17] Other studies[18] estimate the prevalence of prior infection with ehrlichiae to be as high as 7% in selected populations.

Because Rocky Mountain spotted fever, which is transmitted by one of the same tick vectors, is more common in children than in adults,[19] it seems logical that exposures to ehrlichiae occur in childhood. In addition, studies[18,20-22] show that infection with *Rickettsia rickettsii*, the causative agent of Rocky Mountain spotted fever, is probably much more common than disease incidence reports suggest. Despite this, to our knowledge, no studies have looked specifically at the prevalence of ehrlichia antibodies in children living in tick-endemic regions of the country.

Table 1. Age Distribution of the Study Subjects

Age, y	No. (%) of Subjects
1	106 (5)
2	100 (5)
3	81 (4)
4	88 (4)
5	98 (5)
6	116 (6)
7	117 (6)
8	113 (6)
9	120 (6)
10	117 (6)
11	124 (6)
12	119 (6)
13	136 (7)
14	149 (7)
15	146 (7)
16	129 (6)
17	140 (7)
Total	**1999 (99)**

RESULTS

DEMOGRAPHICS

A total of 1999 subjects (1015 male subjects) were studied, distributed as follows: Kansas City, n=194; Little Rock, n=296; Oklahoma City, n=296; Nashville, n=299; Louisville, n=300; Memphis, n=302; and Winston-Salem, n=312. The overall age distribution is given in **Table 1**. Sites differed significantly for the age distribution of the subjects ($P<.001$). For example, in Kansas City, 40% of the subjects were aged 1 to 6 years and 27% were aged 13 to 17 years. By contrast, in Winston-Salem, 18% were aged 1 to 6 years and 46% were aged 13 to 17 years. The sex proportion did not differ significantly between sites ($P=.07$). However, sites differed significantly in racial distribution and in the proportion of subjects living in an urban setting ($P<.001$ for both). Most specimens (68%) were obtained in the outpatient setting (14% at an emergency department visit and 54% from other outpatient settings); the remainder were from children admitted to the hospital. There were significant differences in the relative proportions of these sources between sites ($P<.001$).

SEROLOGICAL RESULTS

Of the 12 randomly included positive control serum samples for *E chaffeensis*, 10 were correctly identified. All 12 *R rickettsii* control serum samples and all 12 negative control serum samples were correctly identified as negative in the *E chaffeensis* IFA. **Figure 1** gives the distribution of *E chaffeensis* titers in the study population. Overall, 250 children (13%) had titers of 1:80 or higher; of these children, only 6 also had antibody to *R rickettsii* at 1:64 or higher, and none had antibody to *R typhi*. Sixty-one children (3%) had ehrlichia titers of 1:160 or higher. As seen in **Figure 2**, age-adjusted seroprevalence rates varied widely between sites. At 1:80 or higher, the highest rate was in Winston-Salem (22%) and the lowest was in Louisville (2%). At 1:160 or higher, the highest rate was in Kansas City (9%) and the lowest was in Oklahoma City (<1%).

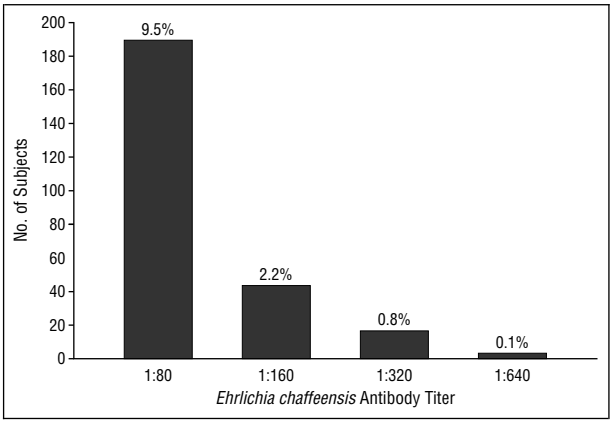

Figure 1. Distribution of positive *Ehrlichia chaffeensis* titers. The percentage of total specimens (N=1999) is shown above the bars.

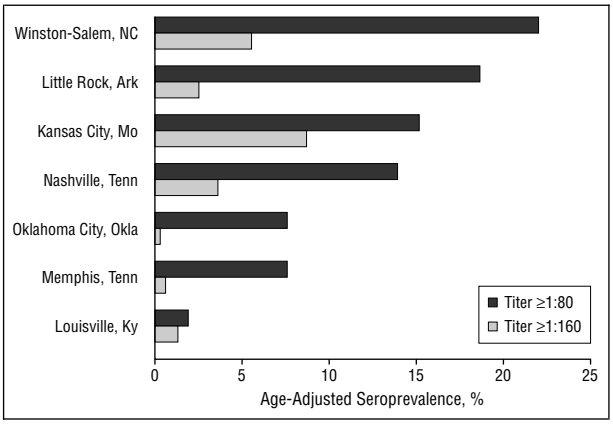

Figure 2. Age-adjusted seroprevalence by site at different cutoff values.

OTHER PREDICTORS

In contingency table analyses, no univariate associations were found between ehrlichia seroprevalence at either cutoff value and sex, race, source of specimen, or residence demographics. Age group was a significant predictor of seroprevalence at both cutoff values. At 1:80 or higher, the seroprevalence was 8% in 1- to 6-year-old subjects, 12% in 7- to 12-year-old subjects, and 18% in 13- to 17-year-old subjects ($P<.001$). At 1:160 or higher, the seroprevalence was 1% in 1- to 6-year-old subjects, 3% in 7- to 12-year-old subjects, and 5% in 13- to 17-year-old subjects ($P<.001$). **Table 2** gives the results of multiple logistic regression analysis at both cutoff values. Study site remained the strongest predictor of seroprevalence. At 1:80 or higher, the odds ratios ranged from 4.2 in Memphis to 15.0 in Winston-Salem (with Louisville as the reference level), and were significant for all sites. At 1:160 or higher, the odds ratios ranged from 1.8 in Memphis to 24.5 in Kansas City (with Oklahoma City as the reference level), and were significant for Nashville, Little Rock, Winston-Salem, and Kansas City. Age remained a significant predictor of seroprevalence at both cutoff values, but only for

Table 2. Multiple Logistic Regression Analysis of Risk Factors for *Ehrlichia chaffeensis* Seropositivity

Factor	Titer* ≥1:80	Titer* ≥1:160
Site		
Louisville, Ky	1.0	3.6 (0.4-32.4)
Memphis, Tenn	4.2 (1.7-10.7)	1.8 (0.2-19.9)
Oklahoma City, Okla	4.6 (1.8-11.5)	1.0
Nashville, Tenn	7.2 (2.9-17.6)	9.6 (1.2-78.6)
Kansas City, Mo	8.9 (3.5-22.5)	24.5 (3.1-191.9)
Little Rock, Ark	11.8 (4.9-28.4)	9.6 (1.2-76.8)
Winston-Salem, NC	15.0 (6.3-35.6)	15.2 (2.0-117.4)
Age, y		
1-6	1.0	1.0
7-12	1.4 (0.9-2.1)	2.1 (0.8-5.5)
13-17	2.4 (1.6-3.5)	4.3 (1.7-10.5)
Source		
Hospital admission	1.0	1.3 (0.7-2.4)
Other outpatient visit	1.0 (0.7-1.4)	1.0
Emergency department visit	1.2 (0.7-1.9)	1.6 (0.7-3.8)
Residence		
Nonurban	1.0	1.0
Urban	1.4 (1.0-1.9)	1.9 (1.0-3.7)
Race		
White	1.0	1.0
Nonwhite	0.9 (0.7-1.3)	1.1 (0.6-2.0)
Sex		
Male	1.0	1.0
Female	1.0 (0.8-1.4)	1.2 (0.7-2.2)

*Data are given as odds ratios (95% confidence intervals). For each variable, the category with the lowest seroprevalence rate was used as the reference level.

the 13- to 17-year-old group. The only other variable to achieve significance in logistic regression was urban residence at the 1:80 or higher cutoff value ($P=.05$).

COMMENT

Tickborne infections have gained public health importance as residential growth has impinged on rural geographic areas and outdoor activities have become more popular.[27,28] Ehrlichiosis is considered one of these emerging zoonoses.[7] The present study shows a high prevalence of IFA antibodies reactive with *E chaffeensis* among children living in the southeast and south-central United States. Even using a stringent cutoff value for positive IFAs, the prevalence of antibody was as high as 9% at one site. The present method does not exclude the possibility that antibodies to cross-reacting ehrlichiae or rickettsiae were detected in some subjects.[7,22,29] Nevertheless, the data suggest that childhood exposures to ehrlichiae are much more common than would be expected from disease incidence reports. It is possible that the antibodies detected herein were generated by infection with related minimally pathogenic ehrlichia species. Alternatively, *E chaffeensis* infection in many children may be subclinical, and the higher reported prevalence of disease in adults may relate to host factors that increase severity.[30] The spectrum of disease may also be broader than previously thought, and symptoms such as fever, headache, malaise, myalgia, anorexia, and rash could be mistaken for self-limited viral syndromes.

The Tick-Borne Infections in Children Study Group

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If such is the case, recognizing and treating mild or early cases might be important in preventing more severe manifestations of disease in some individuals.

The intended sample herein was consecutive children having their blood drawn at each center. The actual sample, however, included only those children with sufficient serum available after clinical tests were performed. This may explain why the age distribution was shifted toward older subjects (Table 1); older subjects may have had more blood obtained and, thus, more was left over for this study. Because many children at all ages were included, it is unlikely this sampling bias affected the results.

The present study was not population based, and the serological methods did not differentiate incident from prevalent infection. Conceivably, some children had their blood drawn because of symptoms suggesting rickettsial infection, although 82% of the serum specimens were collected between February and May, when tickborne diseases are less common. However, because clinical data were not obtained, incident infection cannot be excluded. It is also possible that this study underestimated the true prevalence of ehrlichiosis, because declining antibody titers have been observed after acute infection.[29]

Other biases may have been operative in this convenience sample. For example, children presenting to these regional centers may have been triaged from rural areas, where tick exposures are expected to be more common. On the other hand, hospital admissions might have overrepresented children with chronic conditions that limit mobility and, thus, tick exposure. Alternatively, children with long-term sequelae of ehrlichiosis (eg, neurological damage) might be overrepresented in a hospital-based sample. Emergency department visits might have overrepresented urban children, who are expected to have fewer tick exposures. The impact of these biases, which had competing directions, was minimized in the analysis.

The finding of increasing seroprevalence with age was expected based on the accumulation of exposures over time, and affords internal consistency to the study. The low seroprevalence rate in Louisville was consistent with a low annual reporting rate for disease in Kentucky (0.40 cases per million).[13] The corresponding statewide reporting rates per million for other sites were 5.53 in Arkansas (Little Rock), 4.72 in North Carolina (Winston-Salem), 3.05 in

What This Study Adds

The reported annual incidence of human monocytic ehrlichiosis is low, but serosurveys suggest high infection rates in selected populations. Because children are often exposed to ticks, this study investigated the prevalence of antibody to *E chaffeensis* among children living in endemic regions of the United States.

Overall, 13% of the children had antibody titers of 1:80 or higher and 3% had titers of 1:160 or higher. Age-adjusted seroprevalence rates using the stringent cutoff value were as high as 9% in some areas. Infection with *E chaffeensis* may be more common in children than previously recognized.

Missouri (Kansas City), and 2.90 in Oklahoma (Oklahoma City).[13] Data were not available for Tennessee (Memphis and Nashville). The most unexpected finding in this study was the lack of a strong relationship between nonurban residence and seropositivity. This may have been an artifact of the method used to classify ZIP codes of residence. Some ZIP codes classified as urban in 1990 may have been rural before that. Older children living in those areas may have been more exposed to ticks when they were young, and might carry markers of previous ehrlichia infection despite currently residing in an urban area. Alternatively, living in an urbanized area does not preclude travel to wooded areas. In addition, urbanization per se may not be as important a factor as the local density of foliage and the regional concentration of animal reservoirs. Along these lines, there are reports[31,32] of urban outbreaks of rickettsial diseases and isolated hyperendemic foci.

The data presented herein suggest that infection with *E chaffeensis* or related ehrlichiae is more common in children than would be expected from disease incidence reports. Active population-based surveillance studies are warranted.

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