The Human Ehrlichioses in the United States

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The emerging tick-borne zoonoses human monocytic ehrlichiosis (HME) and human granulocytic ehrlichiosis (HGE) are underreported in the United States. From 1986 through 1997, 1,223 cases (742 HME, 449 HGE, and 32 not ascribed to a specific ehrlichial agent) were reported by state health departments. HME was most commonly reported from southeastern and southcentral states, while HGE was most often reported from northeastern and upper midwestern states. The annual number of reported cases increased sharply, from 69 in 1994 to 364 in 1997, coincident with an increase in the number of states making these conditions notifiable. From 1986 through 1997, 827 probable and confirmed cases were diagnosed by serologic testing at the Centers for Disease Control and Prevention, although how many of these cases were also reported by states is not known. Improved national surveillance would provide a better assessment of the public health importance of ehrlichiosis.

First recognized in the United States in 1986, the human ehrlichioses are considered emerging zoonotic diseases. Two etiologically and epidemiologically distinct forms of illness are recognized: human monocytic ehrlichiosis (HME), caused by *Ehrlichia chaffeensis* (1), and human granulocytic ehrlichiosis (HGE), caused by an agent similar or identical to the veterinary pathogens *E. equi* and *E. phagocytophila* (2). A third species, *E. ewingii*, can also cause human illness (3). The bacteria that cause ehrlichiosis are transmitted to humans through the bite of infected ticks, which acquire the agents after feeding on infected animal reservoirs.

During infection, ehrlichiae form distinctive membrane-bound, intracytoplasmic bacterial aggregates (morulae) in white blood cells. HME is characterized by morulae in monocytes, HGE by morulae in granulocytes. Clinically, HME and HGE are nearly indistinguishable and are characterized by one or more of the following symptoms: fever, headache, myalgia, thrombocytopenia, leukopenia, and elevated liver enzyme levels (4-8). A rash occurs in approximately one third of patients with HME (8) but is less common in patients with HGE (4,9). Most cases of ehrlichiosis are characterized by mild illness. However, complications such as adult respiratory distress syndrome, renal failure, neurologic disorders, and disseminated intravascular coagulation can occur (6,10). Case-fatality ratios are as high as 5% for HME and 10% for HGE (10), although more serious cases are probably overrepresented in these estimates. Other studies have reported case-fatality ratios of <5% for these diseases (4,7).

HME and HGE are most often diagnosed by indirect immunofluorescence assay (IFA), although polymerase chain reaction (PCR) assays are increasingly used (11). A confirmed case is defined as a fourfold change in antibody titer by IFA in acute- and convalescent-phase serum samples, PCR amplification of ehrlichial DNA from a clinical sample, or detection of intraleukocytic morulae and a single IFA titer of ≥ 64. A probable case is defined as a single IFA titer of ≥ 64 or the presence of morulae within infected leukocytes. Laboratory data are only used to support clinical suspicion; the designation of a confirmed or probable case of ehrlichiosis is interpreted in the context of compatible illness (11).

The public health importance of the ehrlichioses has not been well defined, largely because these diseases are newly recognized. Because ehrlichiae are present in blood, concerns have been raised about the risk for perinatal and blood-transfusion transmission

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(12,13). Ehrlichiae are susceptible to tetracyclines, so rapid and effective treatment is possible (8). However, the nonspecific signs and symptoms of these diseases may interfere with timely clinical diagnosis. Ehrlichial infections can be life-threatening. Raising disease awareness and educating physicians and the public about clinical manifestations and proper treatment are indicated.

A national ehrlichiosis surveillance program does not exist, so national incidence rates have not been determined because of wide variability in state surveillance activities. The Council of State and Territorial Epidemiologists recommended that human ehrlichiosis be made nationally notifiable in 1998, but many states do not have a system for surveillance and do not test for ehrlichiosis in state diagnostic laboratories. We summarize the scope of state-supported surveillance efforts and present data on ehrlichiosis cases reported to state health departments from 1986 through 1997. In addition, we include data on ehrlichiosis cases diagnosed by serologic testing at the Centers for Disease Control and Prevention (CDC).

Reported Ehrlichiosis Cases in the United States

From 1986 through 1997, 1,223 ehrlichiosis cases were reported by 30 state health departments in the United States. Data were reported from 19 states that considered ehrlichiosis notifiable as of August 1998, five that routinely collected information on cases, and six that occasionally received reports of ehrlichiosis cases (Appendix I) (14-17). For states where ehrlichiosis was not notifiable, the designation routine reporting versus occasional reporting was based on the completeness of data provided. Because some states did not differentiate between probable and confirmed cases in their records, both categories were considered cases for the purposes of this report. Of the 1,223 reported ehrlichiosis cases, 742 (60.7%) were categorized as HME, 449 (36.7%) as HGE, and 32 (2.6%) as not ascribed to a specific ehrlichial agent. Using data from 20 states that reported information on deaths, we found case-fatality ratios of 2.7% (8 of 299) for HME and 0.7% (3 of 448) for HGE.

HME and HGE Incidence

Data provided through 1997 were used to calculate state-specific average annual incidence rates for 16 of the 19 states that considered ehrlichiosis notifiable and the five states that routinely collected surveillance data (Table). Although Missouri, South Carolina, and Tennessee considered ehrlichiosis notifiable, average annual incidence rates could not be calculated because these states did not differentiate between HME and HGE. Average annual incidence per one million population was calculated by dividing the number of reported cases by the number of years a state collected data (Table). When possible, average annual incidence by county was determined for HME and HGE (Figures 1-2) (15,17).

Table. Average annual ehrlichiosis incidence (per one million population) for reporting states[a] on the basis of 1995 census data (18)

State	Incidence: Human monocytic ehrlichiosis	Incidence: Human granulocytic ehrlichiosis
Arkansas	5.53	0
Arizona	0.12	0
California	0.02	0.03
Connecticut	0.92	15.90
Florida	0.74	0
Illinois	0.11	0.03
Indiana	0.91	0
Kentucky	0.40	0
Maine	0	0
Minnesota	0.22	3.90
Missouri	3.05	0
North Carolina	4.72	0.05
New Hampshire	0	0
New Jersey	1.47	0.17
New York	0.38	2.68
Oklahoma	2.90	0
Pennsylvania	0.01	0.03
Rhode Island	0	0.67
Texas	0.20	0
Virginia	0.68	0
Wisconsin	0	8.79

[a]Includes states that consider ehrlichiosis notifiable, as well as five states where data are routinely collected. Michigan, South Carolina, and Tennessee did not differentiate between cases of human monocytic ehrlichiosis and human granulocytic ehrlichiosis and are not included in this table.

Most HME cases were reported from the southeastern and southcentral areas of the United States (Table, Figure 1). The highest reported average annual incidence rates of HME were in Arkansas (5.53 per million), North Carolina (4.72 per million), Missouri (3.05 per million), and Oklahoma (2.90 per million). In contrast, the highest reported average annual incidence rates

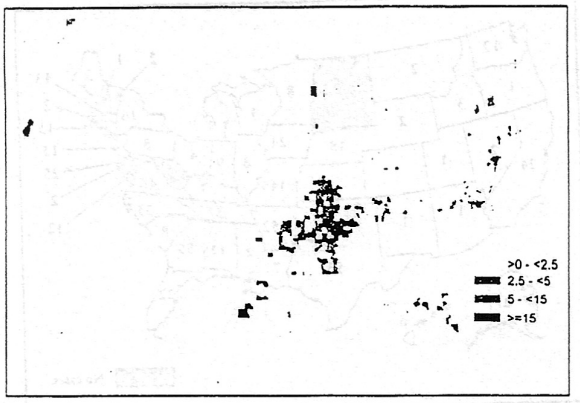

Figure 1. Average annual incidence of reported human monocytic ehrlichiosis (HME) by county, using 1995 population census data (29). Includes states that consider ehrlichiosis notifiable, as well as states that routinely collect information on ehrlichiosis cases. Michigan, South Carolina, and Tennessee are not included because cases of HME and human granulocytic ehrlichiosis were not distinguished by the state health departments. County-specific incidence could not be calculated for North Carolina or Pennsylvania because county of occurrence was not provided by the state health departments.

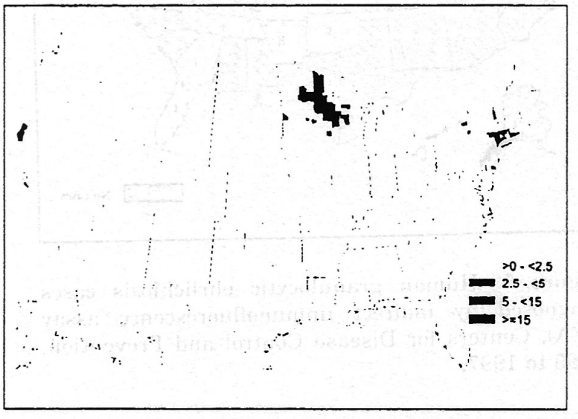

Figure 2. Average annual incidence of reported human granulocytic ehrlichiosis (HGE) by county, using 1995 population census data (29). Includes states that consider ehrlichiosis notifiable, as well as states that routinely collect information on ehrlichiosis cases. Michigan, South Carolina, and Tennessee are not included because cases of human monocytic ehrlichiosis and HGE were not distinguished by the state health departments. County-specific incidence could not be calculated for North Carolina or Pennsylvania because county of occurrence was not provided by the state health departments.

of HGE were in the northeastern and upper midwestern areas of the United States—Connecticut (15.90 per million), Wisconsin (8.79 per million), Minnesota (3.90 per million), and New York (2.68 per million) (Figure 2). The county reporting the highest average annual incidence of HME was Searcy, Arkansas (64.80 per million), and the county with the highest annual incidence of HGE was Jackson, Wisconsin (521.68 per million).

These incidence rates follow the expected geographic distribution of tick vectors for each type of ehrlichiosis. *E. chaffeensis* is primarily transmitted by the lone star tick *(Amblyomma americanum),* which is common in the southeastern United States (19). The black-legged tick *(Ixodes scapularis)* transmits the causative agent of HGE in the northeastern United States (20,21) and the western black-legged tick (*I. pacificus)* in the western coastal United States (22).

Reporting Trends

The annual number of ehrlichiosis cases reported by the state health departments was calculated with data from 18 states that considered ehrlichiosis notifiable as of August 1998 (yearly summaries were not available for Missouri) and the five additional states that routinely collected information on ehrlichiosis cases (Figure 3). The annual number of reported

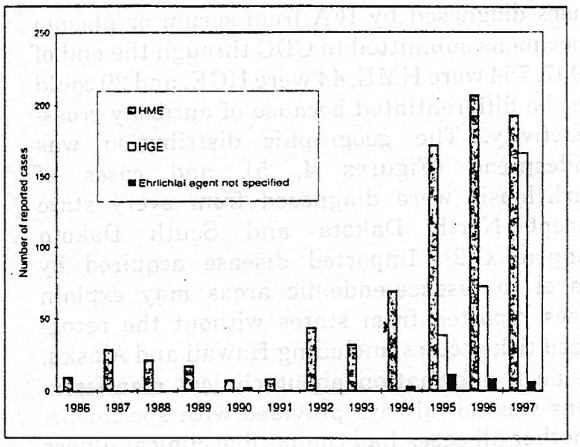

Figure 3. Reported cases of human monocytic ehrlichiosis (HME) and human granulocytic ehrlichiosis (HGE) in the United States, 1986-1997 (includes cases from states that consider ehrlichiosis notifiable, as well as states that routinely collect information). Because yearly summaries of reported cases were not available for Missouri, data from this state are not included. The number of states where ehrlichiosis was notifiable increased from 7 in 1994 to 17 in 1997.

ehrlichiosis cases increased sharply, from 69 in 1994 to 364 in 1997. This increase may be explained by the addition of ehrlichiosis as a notifiable disease in 10 states during this same 4-year interval, the discovery of HGE in 1994, increased availability of diagnostic tests, and increased awareness of ehrlichiosis.

Ehrlichioses Cases Diagnosed at CDC

At CDC, antigen from *E. chaffeensis*, Arkansas strain, is used to diagnose HME by IFA. Before *E. chaffeensis* was isolated in 1991, *E. canis* was used as a surrogate antigen (23). During 1995 to 1996, antigen from *E. equi* obtained from infected horse neutrophils was used, but cases submitted to CDC after 1996 were diagnosed by IFA using cell culture–derived antigen from the HGE agent (24). Antibody from patients with ehrlichial infection may cross-react with both *E. chaffeensis* and the HGE agent (24,25). For patients with significant antibody titers to both *Ehrlichia* species, the causative agent is assumed to be the one with a fourfold or greater change in antibody titer between paired serum samples. If both agents show a fourfold difference, the one with the highest titer is considered the causative agent. If neither shows a fourfold difference, the causative agent is usually not ascribed to a specific ehrlichial species (25).

Of 827 probable and confirmed ehrlichiosis cases diagnosed by IFA from serum or plasma specimens submitted to CDC through the end of 1997, 754 were HME, 44 were HGE, and 29 could not be differentiated because of antibody cross-reactivity. The geographic distribution was widespread (Figures 4, 5), and cases of ehrlichiosis were diagnosed from every state except North Dakota and South Dakota (Appendix 2). Imported disease acquired by travel to disease-endemic areas may explain cases reported from states without the recognized tick vectors, including Hawaii and Alaska. Because information about clinical manifestations was not always provided with specimens, whether all cases had compatible clinical illness is unknown. Of 754 HME cases, 423 (56.1%) were classified as probable and 331 (43.9%) as confirmed on the basis of serologic criteria established by CSTE and CDC (11). In contrast, of 44 HGE cases, 39 (88.6%) were classified as probable and 5 (11.4%) as confirmed.

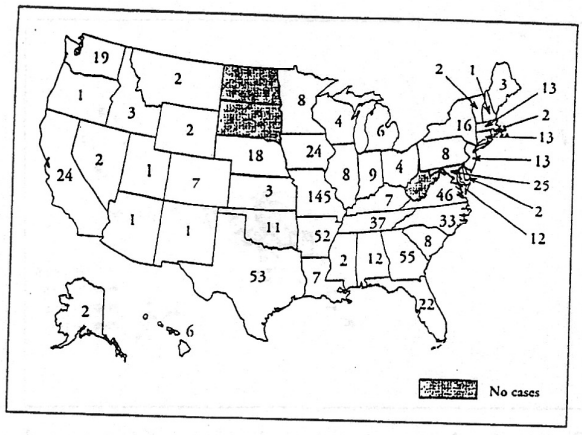

Figure 4. Human monocytic ehrlichiosis cases diagnosed by indirect immunofluorescence assay (IFA), Centers for Disease Control and Prevention, 1986 to 1997.

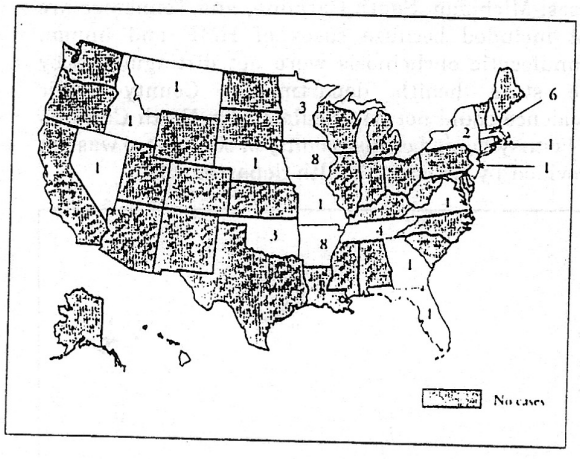

Figure 5. Human granulocytic ehrlichiosis cases diagnosed by indirect immunofluorescence assay (IFA), Centers for Disease Control and Prevention, 1995 to 1997.

Conclusions

Although a few state health departments have published information on local ehrlichiosis surveillance (14-17,26-28), comprehensive national surveillance data had not been collected until this review. This review further defines the public health problem posed by the ehrlichioses in the United States. These diseases have incidence rates comparable with or exceeding those of Rocky Mountain spotted fever in some states (29).

These state-reported data have several limitations. State health departments provided

information on ehrlichiosis cases in different ways. For example, some states provided only data compiled after ehrlichiosis became notifiable, while others provided information as far back as data were available. The ehrlichiosis cases in this article represent a compilation of existing (albeit incomplete) surveillance datasets and probably underestimate the true prevalence of the disease in the United States. Moreover, the accuracy of HME and HGE case-fatality ratios presented here is uncertain. The number of deaths may be underreported because diagnosis of ehrlichiosis requires laboratory confirmation. However, serious or complicated cases, more likely to end in death, are more likely to be investigated and reported to state health departments. The case-fatality ratios described in this article are compatible with findings from other studies (4,7). Finally, the state-reported data include some cases from areas where ehrlichiosis is not commonly diagnosed. For example, a single case of HME was reported from Arizona, although the recognized distribution of the lone star tick does not include this state. Ehrlichiosis cases are usually reported from the patient's county and state of residence at the time of diagnosis; however, ehrlichiosis may be acquired during travel to an area with *Ehrlichia*-infected ticks. Imported cases of ehrlichiosis in states where the disease is not common or tick vectors are absent underscores the need to consider this diagnosis even in areas of low risk.

Diagnostic serologic testing has been offered at CDC since 1986 for HME, and since 1995 for HGE. Records show that from 1986 through 1997 more than 800 ehrlichiosis cases were diagnosed from 48 states. This finding contrasts sharply with state-reported surveillance data, which identified specific geographic regions where ehrlichiosis was most likely to occur.

The number of cases diagnosed at CDC from each state may not accurately reflect expected regional incidence patterns; for example, states with public health laboratories that offer in-house diagnostic tests or states that frequently use commercial laboratories may be less likely to submit samples to CDC for testing. Some cases of ehrlichiosis diagnosed at CDC may also have been reported by state surveillance systems; these reporting systems cannot be regarded as mutually exclusive. The numbers of serologically diagnosed cases of ehrlichiosis reported here may differ from numbers published in other CDC reports because other reports include samples obtained for specific studies (7), whereas most of the cases in this report were submitted for routine diagnostic tests.

As of August 1998, only 19 states considered ehrlichiosis notifiable, and fewer than one fourth of state health departments offered in-house diagnostic assays for HME or HGE. Average annual incidence rates, an important indicator of disease prevalence, could be calculated for only 21 states. These data underscore the need for better nationwide surveillance of ehrlichiosis.

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Dr. McQuiston, a veterinarian, is serving as an Officer in the Epidemic Intelligence Service, Centers for Disease Control and Prevention. Her research focuses on the epidemiologic investigation of several zoonotic pathogens, including rabies virus, ehrlichioses, and *Rickettsia rickettsii*.

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Appendix I: Ehrlichiosis surveillance by state health departments as of August 1998 and total number of cases reported through 1997.

State	First year reportable	Laboratory Tests offered	Human monocytic ehrlichiosis cases	Human granulocytic ehrlichiosis cases	Ehrlichial agent not specified	Total cases
Alabama	Not reportable	None available	--	--	--	--
Alaska	Not reportable	None available	--	--	--	--
Arizona	1997	None available	1	0	0	1
Arkansas	1993	None available	55	0	0	55
California	1996	IFA for both; PCR for both	2	3	0	5
Colorado	Not reportable[a]	None available	--	--	3	3
Connecticut	1995	IFA for both; PCR for both	9	156	9	174
Delaware	Not reportable	None available	--	--	--	--
District of Columbia	Not reportable	None available	--	--	--	--
Florida	1996	IFA for HME only	21	0	0	21
Georgia	Not reportable	None available	--	--	--	--
Hawaii	Not reportable	None available	--	--	--	--
Idaho	Not reportable	None available	--	--	--	--
Illinois	Not reportable[b]	None available	5	1	2	8
Indiana	Not reportable[b]	IFA for HME only	21	0	0	21
Iowa	Not reportable	IFA for both; PCR for both	--	--	--	--
Kansas	Not reportable	None available	--	--	--	--
Kentucky	1989	None available	14	0	0	14
Louisiana	Not reportable[a]	None available	--	--	1	1
Maine	1996	None available	0	0	0	0
Maryland	Not reportable[a]	IFA for both	6	0	1	7
Massachusetts	Not reportable[a]	None available	0	5	0	5
Michigan	1993	None available	--	--	2	2
Minnesota	1996	None available	2	36	0	38
Mississippi	Not reportable[a]	None available	--	--	1	1
Missouri	Reportable, date unknown	None available	162	0	0	162
Montana	Not reportable	None available	--	--	--	--
Nebraska	Not reportable	None available	--	--	--	--
Nevada	Not reportable	None available	--	--	--	--
New Hampshire	1996	None available	0	0	0	0
New Jersey	1995	IFA for both; PCR for both	35	4	0	39
New Mexico	Not reportable[a]	None available	1	0	0	1
New York	1996	IFA for both; PCR for both	28	195	0	223
North Carolina	1998	IFA for HME only	204	1	0	205
North Dakota	Not reportable	None available	--	--	--	--
Ohio	Not reportable	None available	--	--	--	--
Oklahoma	Not reportable[b]	None available	76	0	0	76
Oregon	Not reportable	None available	--	--	--	--
Pennsylvania	1992	None available	1	1	1	3
Rhode Island	1996	None available	0	2	0	2
South Carolina	1990	None available	--	--	5	5
South Dakota	Not reportable	None available	--	--	--	--
Tennessee	1996	IFA for HME only	--	--	7	7
Texas	1996	IFA for HME only; PCR for both	45	0	0	45
Utah	Not reportable	None available	--	--	--	--
Vermont	Not reportable	None available	--	--	--	--
Virginia	Not reportable[b]	None available	54	0	0	54
Washington	Not reportable	None available	--	--	--	--
West Virginia	Not reportable	None available	--	--	--	--
Wisconsin	Not reportable[b]	IFA for both; PCR for HGE only	0	45	0	45
Wyoming	Not reportable	None available	--	--	--	--
Total	n/a	n/a	742	449	32	1,223

[a]Occasionally received reports of ehrlichiosis cases.
[b]Routinely collected information on ehrlichiosis cases.
HME, human monocytic ehrlichiosis; HGE, human granulocytic ehrlichiosis; —, not reported by states; IFA, indirect immunofluorescence assay; PCR, polymerase chain reaction; n/a, not applicable.

Appendix II: Probable and confirmed ehrlichiosis cases diagnosed by indirect immunfluorescence assay (IFA), Centers for Disease Control and Prevention, 1986 through 1997.

State	Human monocytic ehrlichiosis			Human granulocytic ehrlichiosis			Ehrlichial agent not determined[a]			Total cases
	Prob[b]	Conf[c]	Total	Prob[b]	Conf[c]	Total	Prob[b]	Conf[c]	Total	
Alabama	8	4	12	0	0	0	0	1	1	13
Alaska	2	0	2	0	0	0	0	0	0	2
Arizona	0	1	1	0	0	0	0	0	0	1
Arkansas	32	20	52	8	0	8	1	1	2	62
California	15	9	24	0	0	0	0	0	0	24
Colorado	6	1	7	0	0	0	0	0	0	7
Connecticut	9	4	13	0	1	1	0	0	0	14
Delaware	1	1	2	0	0	0	0	0	0	2
District of Columbia	4	8	12	0	0	0	1	0	1	13
Florida	15	7	22	0	1	1	2	1	3	26
Georgia	30	25	55	1	0	1	1	0	1	57
Hawaii	2	4	6	0	0	0	0	0	0	6
Idaho	3	0	3	1	0	1	0	0	0	4
Illinois	3	5	8	0	0	0	0	0	0	8
Indiana	9	0	9	0	0	0	0	0	0	9
Iowa	19	5	24	8	0	8	2	0	2	34
Kansas	1	2	3	0	0	0	0	0	0	3
Kentucky	5	2	7	0	0	0	0	0	0	7
Louisiana	5	2	7	0	0	0	0	0	0	7
Maine	2	1	3	0	0	0	0	0	0	3
Maryland	18	7	25	0	0	0	1	1	2	27
Massachusetts	10	3	13	5	1	6	1	1	2	21
Michigan	4	2	6	0	0	0	0	0	0	6
Minnesota	5	3	8	0	0	0	0	0	0	8
Mississippi	0	2	2	0	0	0	0	0	0	2
Missouri	61	84	145	0	1	1	2	2	4	150
Montana	2	0	2	1	0	1	0	0	0	3
Nebraska	17	1	18	1	0	1	0	1	1	20
Nevada	0	1	1	1	0	1	0	0	0	2
New Hampshire	1	0	1	0	0	0	0	0	0	1
New Jersey	4	9	13	1	0	1	0	0	0	14
New Mexico	1	0	1	0	0	0	0	0	0	1
New York	13	3	16	2	0	2	0	0	0	18
North Carolina	28	5	33	0	0	0	1	1	2	35
North Dakota	0	0	0	0	0	0	0	0	0	0
Ohio	4	0	4	0	0	0	0	0	0	4
Oklahoma	4	7	11	3	0	3	0	1	1	15
Oregon	0	1	1	0	0	0	0	0	0	1
Pennsylvania	2	6	8	0	0	0	0	0	0	8
Rhode Island	2	0	2	0	0	0	0	0	0	2
South Carolina	4	4	8	0	0	0	0	0	0	8
South Dakota	0	0	0	0	0	0	0	0	0	0
Tennessee	15	22	37	4	0	4	2	0	2	43
Texas	22	31	53	0	0	0	0	0	0	53
Utah	0	1	1	0	0	0	0	0	0	1
Vermont	2	0	2	0	0	0	0	0	2	4
Virginia	17	29	46	1	0	1	2	0	2	49
Washington	13	6	19	0	0	0	0	0	0	19
West Virginia	0	0	0	0	0	0	0	1	1	1
Wisconsin	3	1	4	2	1	3	1	1	2	9
Wyoming	0	2	2	0	0	0	0	0	0	2
Total	423	331	754	39	5	44	17	12	29	827

[a]Includes cases that could not be ascribed to a specific ehrlichial agent because of antibody cross-reactivity.
[b]Probable case (single antibody titer of ≥ 64 by IFA).
[c]Confirmed case (fourfold change in antibody titer in paired serum samples by IFA).