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Increasing Incidence of *Ehrlichia chaffeensis* and *Anaplasma phagocytophilum* in the United States, 2000–2007

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Abstract. *Ehrlichia chaffeensis* causes human monocytic ehrlichiosis, and *Anaplasma phagocytophilum* causes human granulocytic anaplasmosis. These related tick-borne rickettsial organisms can cause severe and fatal illness. During 2000–2007, the reported incidence rate of *E. chaffeensis* increased from 0.80 to 3.0 cases/million persons/year. The case-fatality rate was 1.9%, and the hospitalization rate was 49%. During 2000–2007, the reported incidence of *A. phagocytophilum* increased from 1.4 to 3.0 cases/million persons/year. The case-fatality rate was 0.6%, and the hospitalization rate was 36%. Rates among female patients were lower than among male patients for ehrlichiosis (rate ratio = 0.68) and anaplasmosis (rate ratio = 0.70). Most (80%) ehrlichiosis and anaplasmosis cases met only a probable case definition, although, use of a polymerase chain reaction to confirm infections increased during 2000–2007. Heightened reporting of these diseases will likely continue with improving recognition, changing surveillance practices, and appropriate application of diagnostic assays.

INTRODUCTION

Ehrlichiosis and anaplasmosis are tick-borne illnesses caused by obligate intracellular bacteria of the genera *Ehrlichia* and *Anaplasma*, respectively. Although suspected cases were previously reported, the first case of human monocytic ehrlichiosis was documented in a patient at Fort Chaffee, Arkansas in 1991, and the causative agent was named *Ehrlichia chaffeensis*.[1–3] Human granulocytic infections by *Anaplasma* were first reported in patients from Wisconsin and Minnesota in 1994.[4–6] Originally classified under the genus *Ehrlichia*, the causative agent of human granulocytic ehrlichiosis was later determined to be the same agent as *Ehrlichia phagocytophila* and *Ehrlichia equi*. All three agents were reclassified under the species *Anaplasma phagocytophilum* in 2001.[7] *Ehrlichia ewingii* was first identified as an agent of human disease from four residents of Missouri.[8]

Clinical presentations of ehrlichiosis and anaplasmosis are similar and nonspecific.[9] Symptoms frequently include fever, chills, headache, myalgia, and nausea. Up to 30% of patients and 60% of children infected with *E. chaffeensis* have a rash; a rash is less commonly reported in *A. phagocytophilum* patients.[10,11] Laboratory findings associated with ehrlichiosis and anaplasmosis include leukopenia, thrombocytopenia, elevated serum aminotransferase levels, and elevated creatinine levels.[9–11] Patients treated with tetracycline typically recover quickly, and surveillance reports have indicated that the overall case-fatality rate was low.[12,13] Complications can be severe and include adult respiratory distress syndrome, disseminated intravascular coagulopathy, central nervous system involvement, and renal failure.[9,12]

Human cases are associated with exposure to ticks. The Lone Star tick, *Amblyomma americanum*, maintains the enzootic cycle of *E. chaffeensis* primarily among white-tailed deer (*Odocoileus virginianus*).[14–16] The intersection of the vector and the reservoir of *E. chaffeensis* occurs largely in the southeastern and south-central United States.[17,18] *Ehrlichia ewingii* may be maintained in a similar enzootic cycle, with deer and domestic dogs proposed as possible reservoir species.[19–21] Small mammals are the primary reservoir for *A. phagocytophilum*, and the vectors *Ixodes scapularis* (black-legged or deer tick) and *Ixodes pacificus* (western black-legged tick) maintain *A. phagocytophilum* prevalence primarily in the northeastern, the upper midwestern, and the Pacific coast regions.[16,17,22,23] Previous surveillance summaries found most cases reported within these areas.[12,13]

In 2000, the Council of State and Territorial Epidemiologists (CSTE) published surveillance case definitions for infection by *E. chaffeensis* and *A. phagocytophilum*.[24] A third reportable category for Undetermined, Unspecified, or Other Agent (UUOA) captured cases where available laboratory evidence was insufficient to specify the causative agent and cases where the causative agent was specified as an agent other than *E. chaffeensis* or *A. phagocytophilum*. These three surveillance case definitions were used until January 2008, when the CSTE implemented new case definitions.[25] We summarize ehrlichiosis and anaplasmosis surveillance data reported to the Centers for Disease Control and Prevention (CDC) during 2000–2007.

METHODS

National surveillance systems. Individual state and territory health departments report surveillance data to CDC through the National Electronic Telecommunications System for Surveillance (NETSS) and through manually completed Case Report Forms (CRFs). NETSS captures demographics such as county of residence, sex, race group, Hispanic ethnicity, and age. These data are used to calculate reported incidence rates across demographics and time. Cases are reported as either probable or confirmed by the State or Local Public Health Departments. Reports from California do not differentiate between probable and confirmed cases.

The CRFs capture additional data on clinical presentation, clinical course, laboratory data, and patient outcome. These data from CRFs are used to calculate descriptive statistics supplementing the NETSS data. The quality of the data from both systems varies by state and locality. Clinicians must make accurate diagnoses, request appropriate laboratory assays, and

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report sufficient information before a case may be classified according to the CSTE definitions.

The data presented in this report differ from the data presented in the Morbidity and Mortality Weekly Report (MMWR) annual summaries; the MMWR lists cases by report date whereas this analysis uses date of onset when available. Also, the reportable category UUOA was not published in the MMWR during 2000–2004. However, these reported cases are included in this analysis.

Analytical and statistical methods. Confirmed and probable cases reported through NETSS with an event date during 2000–2007 were used as the numerator for calculating reported incidence rates. Reported incidence was calculated as a rate per million persons per year (PY) by using population estimates from the United States Census Bureau for each county and for both sexes.[26,27] Because of the large proportion of cases with missing race and ethnicity information in the NETSS data, comparisons of rates between races and ethnic groups were omitted. Cases reported through the CRFs were included in this analysis if the onset date was during 2000–2007 and the cases met confirmed or probable case definition. All analyses were performed using SAS® software.[28] Because these results were calculated from all reported cases, the sampling fraction was one, and statistical tests of significance and confidence intervals were not included.

Reporting states. States that did not consider the disease reportable for a given year were excluded from that year's analysis. During 2000–2007, *E. chaffeensis* and *A. phagocytophilum* were not reportable through NETSS for Alaska (2000–2001, 2005–2007), Colorado (2000–2003, 2005, 2007), Washington, DC (2000, 2003–2005, 2007), Hawaii (2000, 2006–2007), Iowa (2005–2007), Idaho (2000–2001, 2005–2007), Illinois (2000), Louisiana (2000–2001, 2003–2005), Maryland (2000–2001), Mississippi (2001, 2007), Montana (2000–2001, 2006–2007), North Dakota (2000–2005, 2007), New Mexico (2000–2001, 2007), Nevada (2000, 2005, 2007), Oregon (2000), Pennsylvania (2003–2004), Vermont (2000), and Washington (2006–2007).

During 2000, the UUOA category was reportable through NETSS only in New York. During 2001–2007, this category was not reportable for Alaska (2001, 2005–2007), Colorado (2001–2003, 2005, 2007), Washington, DC (2003–2006, 2007), Hawaii (2006–2007), Iowa (2005–2007), Idaho (2001, 2005–2007), Louisiana (2003–2005), Maryland (2001), Mississippi (2001, 2007), Montana (2001, 2006–2007), North Dakota (2001–2005, 2007), Nebraska (2007), New Jersey (2005–2006), New Mexico (2001, 2007), Nevada (2005, 2007), Pennsylvania (2003–2004), and Washington (2006–2007).

RESULTS

Ehrlichia chaffeensis. During 2000–2007, a total of 3,126 cases of *E. chaffeensis* were reported through NETSS (Table 1). The national reported incidence rate was 1.4 cases per million PY. Reported incidence rates by state (Table 2) and county (Figure 1A) indicate endemic disease in southeastern and south-central United States, especially in Central and Atlantic census regions. Reported incidence increased during the study period from 0.80 cases per million PY during 2000 to 3.0 cases per million PY during 2007 (Figure 2).

Reported rates among female patients (rate ratio [RR] = 0.68) were lower than among male patients. Reported incidence rates increased with age (Figure 3), and rates among persons 60–69 years of age (RR = 2.4) were the highest compared with the entire population. Reported cases were primarily among persons of white race and non-Hispanic ethnicity (Table 1). Of the 2,365 reported cases with a date for onset of symptoms (Figure 4), reporting peaked in the summer months from June through August (n = 1,458, 62%), and the fewest cases were reported during the winter months of December, January, or February (n = 75, 3.2%).

During the same study period 1,206 cases of *E. chaffeensis* were reported to CDC via CRFs (Table 1), of which 240 (20%) were classified as confirmed cases. Among cases reporting hospitalization status (Table 3), 570 (49%) were

Table 1

Demographics profiles and case classification for *Ehrlichia chaffeensis*, *Anaplasma phagocytophilum*, and undetermined, unknown or other agent (UUOA) as reported to the National Electronic Telecommunications System for Surveillance (NETSS) and Case Report Forms (CRFs), United States, 2000–2007

	NETSS			CRFs		
	E. chaffeensis, n = 3,126, no. (%)	*A. phagocytophilum*, n = 4,271, no. (%)	UUOA, n = 824, no. (%)	*E. chaffeensis*, n = 1,206, no. (%)	*A. phagocytophilum*, n = 2,040, no. (%)	UUOA, n = 656, no. (%)
Case classification	3,122 (99.9)	4,267 (99.9)	814 (98.8)			
Confirmed	875 (28.0)	1,307 (30.6)	261 (31.1)	240 (19.9)	437 (21.4)	113 (17.2)
Probable	2,247 (72.0)	2,960 (69.4)	553 (67.9)	966 (80.1)	1,603 (78.6)	543 (82.8)
Sex	3,100 (99.2)	4,123 (96.5)	823 (99.9)	1,189 (98.6)	1,994 (97.7)	656 (100)
Male	1,820 (58.7)	2,396 (58.1)	475 (57.7)	717 (60.3)	1,205 (60.4)	374 (57)
Female	1,280 (41.3)	1,727 (41.9)	348 (42.3)	472 (39.7)	789 (39.6)	282 (43)
Race	2,340 (74.9)	2,267 (53.1)	711 (86.3)	1,004 (83.3)	1,084 (53.1)	609 (92.8)
White	2,201 (94.1)	2,200 (97)	682 (95.9)	920 (91.6)	1,051 (97)	590 (96.9)
Black	77 (3.3)	29 (1.3)	17 (2.4)	31 (3.1)	10 (0.9)	7 (1.1)
American Indian*	57 (2.4)	21 (0.9)	12 (1.7)	53 (5.3)	17 (1.6)	5 (0.8)
Asian†	5 (0.2)	17 (0.7)	0 (0)	0 (0)	6 (0.6)	7 (1.1)
Ethnicity	2,060 (65.9)	1,598 (37.4)	673 (81.7)	899 (74.5)	909 (44.6)	585 (89.2)
Hispanic	64 (3.1)	59 (3.7)	44 (6.5)	19 (2.1)	17 (1.9)	35 (6)
Non-Hispanic	1,996 (96.9)	1,539 (96.3)	629 (93.5)	880 (97.9)	892 (98.1)	550 (94)
Age (years)						
Mean	50.1	52.2	50.5	46.8	49.4	50.4
Median	52	54	54	51	53	54

* Or Alaskan Native.
† Or Pacific Islander.

TABLE 2
Cases and incidence rates for *Ehrlichia chaffeensis*, *Anaplasma phagocytophilum*, and undetermined, unknown, or other agent (UUOA) as reported to the National Electronic Telecommunications System for Surveillance, United States, 2000–2007

Region	*E. chaffeensis*		*A. phagocytophilum*		UUOA	
	No. cases	Rate*	No. cases	Rate*	No. cases	Rate*
New England	167	1.5	1,006	8.9	26	0.3
Connecticut	2	0.1	362	13.1	–	–
Massachusetts	80	1.6	333	6.5	2	< 0.1
Maine	9	0.9	31	3.0	2	0.2
New Hampshire	8	0.8	4	0.4	1	0.1
Rhode Island	67	7.9	273	32.1	21	2.8
Vermont	1	0.2	3	0.7	–	–
Mid Atlantic	650	2.2	1,351	4.6	34	0.1
New Jersey	222	3.2	152	2.2	1	< 0.1
New York	424	2.8	1,189	7.7	17	0.1
Pennsylvania	4	0.1	10	0.1	16	0.3
West north central	641	4.5	1,303	9.1	63	0.5
Iowa	–	–	1	0.1	–	–
Kansas	7	0.3	3	0.1	1	0.1
Minnesota	109	2.7	1,223	30.2	1	< 0.1
Missouri	523	11.4	71	1.5	60	1.5
North Dakota	–	–	–	–	–	–
Nebraska	2	0.1	5	0.4	1	0.1
South Dakota	–	–	–	–	–	–
East north central	117	0.3	392	1.1	479	1.5
Illinois	77	0.9	18	0.2	28	0.3
Indiana	11	0.2	2	< 0.1	1	< 0.1
Michigan	3	< 0.1	3	< 0.1	2	< 0.1
Ohio	16	0.2	9	0.1	1	< 0.1
Wisconsin	10	0.2	360	8.2	447	11.6
South Atlantic	708	1.7	121	0.3	112	0.3
Washington, DC	–	–	–	–	–	–
Delaware	38	5.8	24	3.6	–	–
Florida	61	0.4	13	0.1	–	–
Georgia	78	1.1	7	0.1	1	< 0.1
Maryland	229	6.9	33	1.0	59	1.8
North Carolina	237	3.5	24	0.4	12	0.2
South Carolina	17	0.5	10	0.3	7	0.2
Virginia	45	0.8	10	0.2	33	0.6
West Virginia	3	0.2	–	–	–	–
East south central	259	1.9	25	0.2	27	0.2
Alabama	22	0.6	11	0.3	2	0.1
Kentucky	24	0.7	1	< 0.1	3	0.1
Mississippi	–	–	–	–	–	–
Tennessee	213	4.5	13	0.3	22	0.5
West south central	577	2.4	64	0.3	72	0.3
Arkansas	225	10.3	18	0.8	17	0.9
Louisiana	1	0.1	–	–	1	0.1
Oklahoma	338	12	44	1.6	1	< 0.1
Texas	13	0.1	2	< 0.1	53	0.3
Mountain	3	< 0.1	2	< 0.1	1	< 0.1
Arizona	1	< 0.1	1	< 0.1	–	–
Colorado	–	–	–	–	–	–
Idaho	–	–	–	–	–	–
Montana	–	–	–	–	–	–
New Mexico	1	0.1	–	–	–	–
Nevada	1	0.1	1	0.1	–	–
Utah	–	–	–	–	–	–
Wyoming	–	–	–	–	1	0.3
Pacific	4	< 0.1	7	< 0.1	10	< 0.1
Alaska	–	–	–	–	–	–
California	4	< 0.1	4	< 0.1	10	< 0.1
Hawaii	–	–	–	–	–	–
Oregon	–	–	3	0.1	–	–
Washington	–	–	–	–	–	–

*Incidence rate per million persons per year.

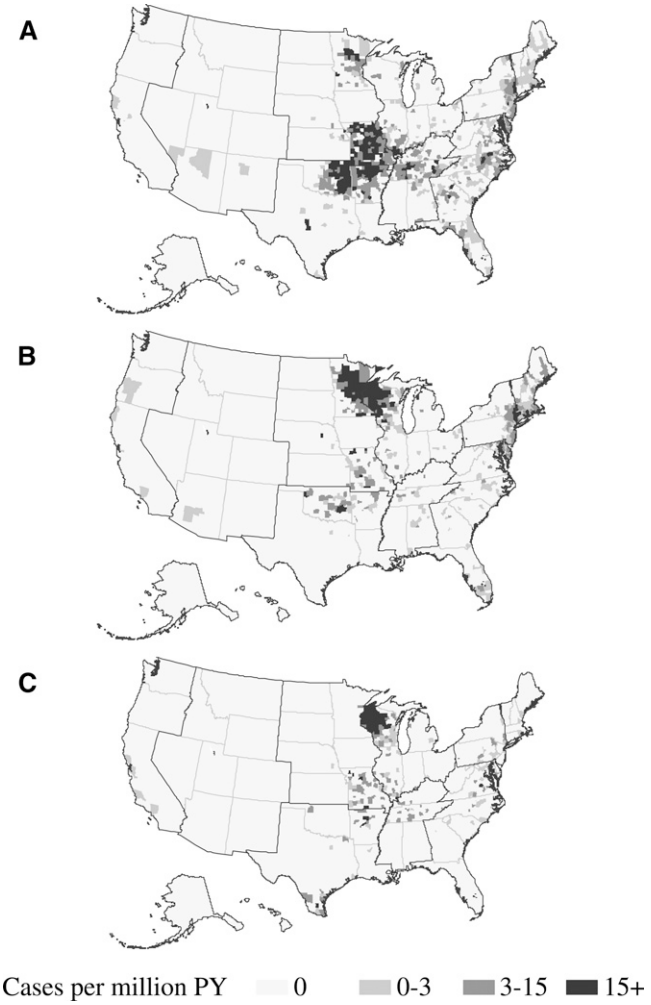

FIGURE 1. County level incidence rates of **A**, *Ehrlichia chaffeensis* (n = 3,116), **B**, *Anaplasma phagocytophilum* (n = 4,116), and **C**, undetermined, unspecified, or other agent (n = 819) as reported to the National Electronic Telecommunications System for Surveillance, United States, 2000–2007. Incidence rates are cases per million persons per year.

hospitalized during the course of illness. A higher proportion was hospitalized among persons 60–69 years of age (54%) and persons ≥ 70 years of age (71%) than among other age groups (Figure 5). Of the cases reporting clinical outcome (Table 3), there were 19 fatal cases (1.9%). Case-fatality rates were higher among persons 5–9 years of age (3.7%), 60–69 years of age (2.5%) and ≥ 70 years of age (3.5%) than among other age groups. The median time between onset and death was 11 days (range = 7–32 days). There were 113 cases (9.2%) for which life-threatening complications were reported (Table 4).

Among those reporting immune status (n = 742), 89 cases (12%) reported immunosuppressive conditions, including 17 cases (2.3%) with cancer, 12 cases (1.6%) with diabetes, 8 cases (1%) with arthritis, and 5 cases (0.7%) with a history of organ transplantation. The median age of those with an immunosuppressive condition was 58 years, and the median age among immunocompetent persons was 53 years. The clinical course was worse for immunosuppressed cases relative to immunocompetent cases when the outcomes hospitalization (RR = 1.8), a life-threatening complication (RR = 2.5), and death (RR = 3.7) were used.

Most *E. chaffeensis* cases were diagnosed by using indirect immunofluorescence assays (IFAs) specific for IgG (n = 880, 73%). However, only a small number of these serologic diagnoses (n = 97, 11%) demonstrated seroconversion and

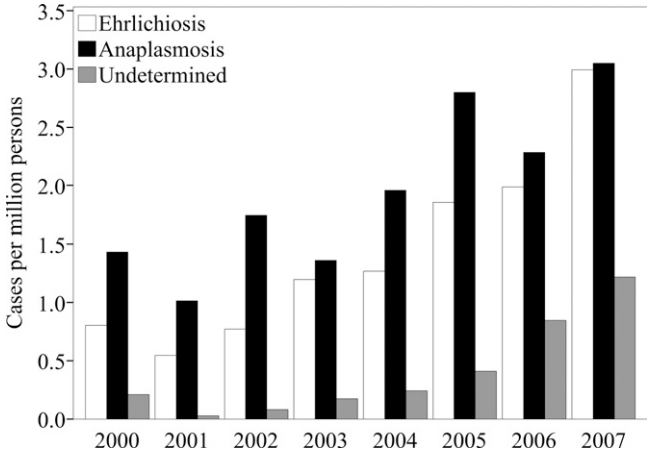

FIGURE 2. Annual incidence rates of *Ehrlichia chaffeensis* (n = 3,126), *Anaplasma phagocytophilum* (n = 4,271), and undetermined, unspecified, or other agent (n = 824) as reported to the National Electronic Telecommunications System for Surveillance, United States, 2000–2007. Incidence rates are cases per million persons per year.

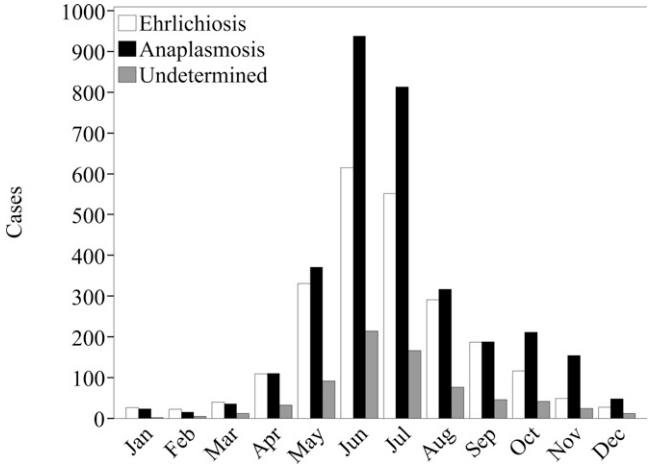

FIGURE 4. Case counts by month of onset of *Ehrlichia chaffeensis* (n = 2,365), *Anaplasma phagocytophilum* (n = 3,224), and undetermined, unspecified, or other agent (n = 723) as reported to the National Electronic Telecommunications System for Surveillance, United States, 2000–2007.

were classified as confirmed cases. A positive, acute-phase serologic result was the only supporting laboratory evidence for 876 cases (73%). A total of 131 cases of *E. chaffeensis* cases (10.9%) were confirmed by polymerase chain reaction (PCR). The proportion of cases confirmed by PCR increased from less than 10% during 2000–2005 to 20% in 2007 (Figure 6A).

Anaplasma phagocytophilum. During 2000–2007, a total of 4,271 cases of *A. phagocytophilum* were reported through NETSS (Table 1). The national reported incidence rate was 2.0 cases per million PY. Reported incidence rates by state (Table 2) and county (Figure 1B) identified endemic disease transmission in the New England, mid Atlantic, and Western north central census regions. Reported incidence increased from 1.4 cases per million PY during 2000 to 3.0 cases per million during 2007 (Figure 2). Reported rates among female patients (RR = 0.70) were lower than among male patients. Reported incidence rates increased with age (Figure 3), and the highest rate was among persons 60–69 years of age (RR = 2.4). Most cases were reported as white race group and non-Hispanic ethnicity (Table 1). Of the 3,224 cases with a reported onset date (Figure 4), the largest number of cases (n = 2,068, 64%) were during the summer months of June through August, and 86 cases of anaplasmosis (2.7%) reported an onset during the winter months of December, January, or February.

During the study period 2,040 cases of *A. phagocytophilum* were reported to CDC via CRFs meeting the CSTE case definition (Table 1); 437 cases (21%) met the CSTE case definition for confirmed anaplasmosis. Of those reporting hospitalization statuses (Table 3), 687 cases (36%) were hospitalized. A higher proportion of cases were hospitalized among persons ≥ 70 years of age (65%), followed by persons 60–69 years of age (42%) and 5–9 years of age (42%) (Figure 5). Of the cases reporting a clinical outcome (Table 3), there were 11 fatal cases (0.6%). Case-fatality rates were highest among persons 20–39 years of age (1.2%). The median time between onset and death was 8.5 days (range = 2–36 days). Of those

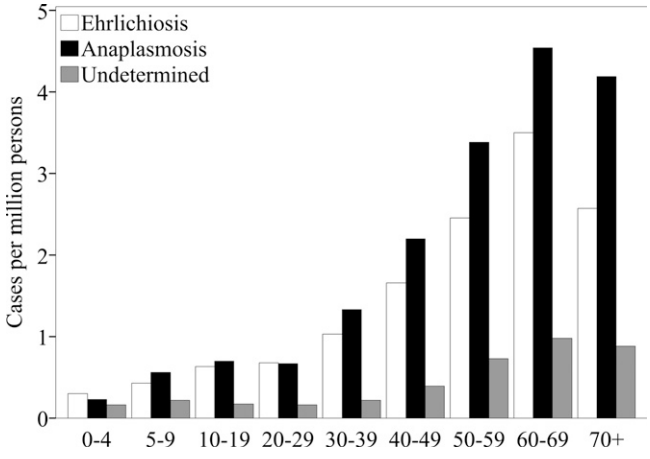

FIGURE 3. Incidence rates by age group of *Ehrlichia chaffeensis* (n = 3,103), *Anaplasma phagocytophilum* (n = 4,135), and undetermined, unspecified, or other agent (n = 782) as reported to the National Electronic Telecommunications System for Surveillance, United States, 2000–2007. Incidence rates are cases per million persons per year.

TABLE 3

Hospitalization and outcome for cases of *Ehrlichia chaffeensis*, *Anaplasma phagocytophilum*, and undetermined, unknown, or other agent (UUOA) as reported through Case Report Forms, United States, 2000–2007

Characteristic	*E. chaffeensis*, n = 1,206, no. (%)	*A. phagocytophilum*, n = 2,040, no. (%)	UUOA, n = 656, no. (%)
Reporting			
Hospitalization	1,173 (97.3)	1,907 (93.5)	638 (97.3)
Hospitalized	570 (48.6)	687 (36.0)	225 (35.3)
Confirmed	169 (29.6)	163 (23.7)	51 (22.7)
Probable	401 (70.4)	524 (76.3)	174 (77.3)
Not hospitalized	603 (51.4)	1220 (64.0)	413 (64.7)
Confirmed	63 (10.4)	218 (17.9)	55 (13.3)
Probable	540 (89.6)	1,002 (82.1)	358 (86.7)
Reporting			
Outcome	1,027 (85.2)	1,921 (94.2)	642 (97.9)
Died	19 (1.9)	11 (0.6)	3 (0.5)
Confirmed	8 (42.1)	2 (18.2)	0 (0)
Probable	11 (57.9)	9 (81.8)	3 (100)
Survived	1,008 (98.1)	1,910 (99.4)	639 (99.5)
Confirmed	215 (21.3)	380 (19.9)	109 (17.1)
Probable	793 (78.7)	1,530 (80.1)	530 (82.9)

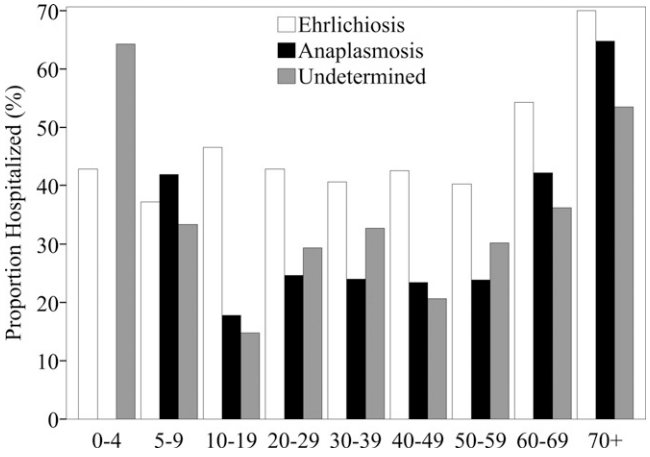

FIGURE 5. Proportion of cases hospitalized by age group of *Ehrlichia chaffeensis* (n = 1,141), *Anaplasma phagocytophilum* (n = 1,827), and undetermined, unspecified, or other agent (n = 630) as reported through Case Report Forms, United States, 2000–2007.

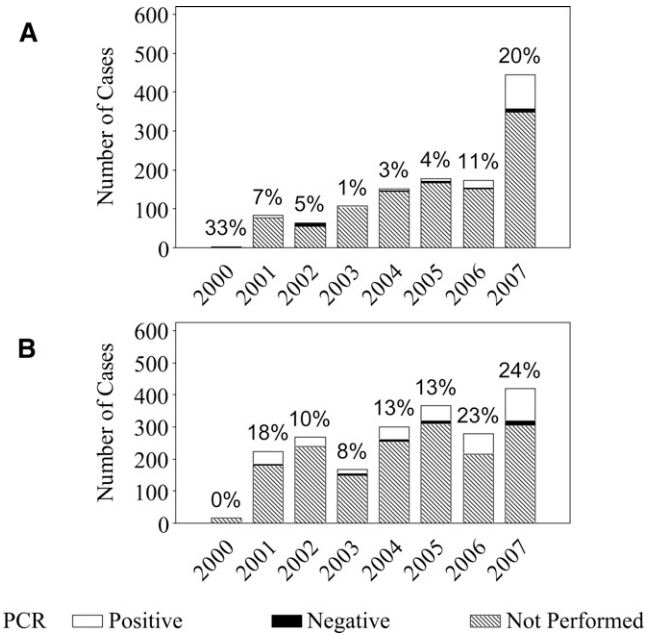

FIGURE 6. Number of annual cases of **A**, *Ehrlichia chaffeensis* (n = 1,191) and **B**, *Anaplasma phagocytophilum* (n = 2,035), reported through Case Report Forms (CRFs), United States, 2000–2007. The annual number of cases are subdivided into polymerase chain reaction (PCR)–positive cases, PCR-negative cases, and cases in which PCR was not performed. The annotation above each vertical bar is the annual percent of reported cases diagnosed by using PCR. Because the Centers for Disease Control and Prevention began collecting CRFs in 2000, few cases were reported in 2000.

cases reporting complications, 60 (3.0%) reported developing life-threatening complications (Table 4).

Of the cases reporting immune status (n = 1,943), 79 (6.5%) reported immunosuppressive conditions, including 15 cases (0.77%) with cancer, 9 cases with diabetes (0.5%), 5 cases (0.2%) with arthritis, and 4 cases (0.2%) with asplenia. The median age among those reporting an immunosuppressive condition was 65.5 years, and the median age among immunocompetent persons was 54 years. The clinical course was worse for immunosuppressed cases relative to immunocompetent cases when the outcomes hospitalization (RR = 1.9), a life-threatening complication (RR = 2.8), and death (RR = 3.9) were used.

A total of 1,080 cases (53%) relied on a single positive serologic test result for supporting laboratory evidence. Most *A. phagocytophilum* cases were reported with only IFA IgG (n = 1,068, 52%) as supporting laboratory evidence. However, only a small number of these serologic diagnoses (n = 89, 8.3%) demonstrated seroconversion on IFA and were classified as confirmed cases. A small proportion of *A. phagocytophilum* cases (n = 334, 16%) were confirmed by means of PCR. However, the proportion of PCR-positive cases increased in 2006 and 2007 (Figure 6B).

Undetermined, unspecified, or other agent. During 2000–2007 a total of 824 cases of UUOA were reported through the NETSS (Table 1). Although this category included possible reports of *E. ewingii* during the study period, this category was most frequently used by states to report cases for which the causative agent could not be definitively identified or for which a conclusive assay was not available. The national reported incidence of UUOA cases was 0.42 cases per million PY. Reported incidence rates of UUOA were highest in states where *A. phagocytophilum* was endemic during the same time period (Table 2, Figure 1C). Reporting under this category increased from 0.21 cases per million PY during 2000 up to 1.2 cases per million PY during 2007 (Figure 2). Reported incidence rates for the UUOA category increased with age similar to those for ehrlichiosis and anaplasmosis (Figure 3). Reported rates among female patients (RR = 0.71) were lower than among male patients. Cases were predominantly reported for the white race group and non-Hispanic ethnicity (Table 1). Of the 723 cases with reported onset dates (Figure 4), 456 cases (63%) became symptomatic during the summer months from June through August.

A total of 656 cases of UUOA were reported to CDC via CRFs (Table 1), including 113 (17%) that met a confirmed case definition. Among these cases of UUOA, nine cases (1%) of *E. ewingii* were reported from Missouri (n = 8) and Minnesota (n = 1). The single *E. ewingii* case reported from Minnesota was later determined to be a species of *Ehrlichia* distinct from *E. ewingii* and E. *chaffeensis* (McFadden JW and others, International Conference of Emerging Infectious Diseases, 2010). Among UUOA cases reporting hospitalization status (Table 3), 225 cases (35%) were hospitalized. The proportion hospitalized was highest among persons < 5 year of age (64%) and ≥ 70 years of age (53%) (Figure 5). Of the

TABLE 4

Reports of life-threatening complications during the clinical course of *Ehrlichia chaffeensis*, *Anaplasma phagocytophilum*, and undetermined, unknown, or other agent (UUOA) as reported through Case Report Forms, United States, 2000–2007*

Complication	*E. chaffeensis*, n = 113, no. (%)	*A. phagocytophilum*, n = 60, no. (%)	UUOA, n = 51, no. (%)
ARDS†	20 (18.2)	8 (13.3)	7 (13.7)
DIC‡	14 (12.7)	2 (3.3)	4 (7.8)
Meningitis/encephalitis	32 (29.1)	5 (8.3)	14 (27.5)
Renal failure	34 (30.9)	12 (20)	14 (27.5)
Other	48 (43.6)	37 (61.7)	27 (52.9)

*Percentages are based on the proportion of patients reported with any life-threatening illness. Overall reports of life-threatening illness were low, and details regarding how a specific diagnosis (such as DIC or ARDS) was made were not acquired. Data include confirmed and probable cases.

†ARDS = adult respiratory distress syndrome.

‡DIC = disseminated intravascular coagulopathy.

cases reporting clinical outcome (Table 3), there were 3 fatal cases (0.5%); all fatal cases were in adults ≥ 40 years of age. The median time between onset and death was 6 days (range = 5–7 days). Life-threatening complications were reported for 51 cases (7.8%) (Table 4).

Among those with reported immune status (n = 525), 71 cases (14%) reported some immunosuppressive condition, including 10 cases (1.9%) with diabetes, 8 cases (2%) with cancer, 5 cases (1%) with arthritis, and 5 cases (1%) with chronic obstructive pulmonary disease. The hospitalization RR comparing immunosuppressed cases and immunocompetent cases was 1.9, and the RR of life-threatening complications was 2.8. There were no deaths reported among immunosuppressed cases. A total of 278 cases (42%) were diagnosed by using only a single, positive laboratory serologic titer determined by IFA.

DISCUSSION

Geography plays an important role in the epidemiology of ehrlichiosis and anaplasmosis infections. During 2000–2007, the Ozark Mountains and the Eastern Seaboard regions reported high incidence rates of *E. chaffeensis* infection. Similarly, the Northern Midwest and the Northern Atlantic Seaboard regions reported high incidence rates of *A. phagocytophilum* infection. These spatial trends are consistent with the epizoology of these pathogens, which are transmitted by distinct tick species with defined geographic ranges and host preferences.[16] National surveillance for these diseases is important for several reasons: assessment of the overall burden of tick-borne disease as an important public health problem, detection of the emergence of novel related pathogens in unexpected areas, and monitoring for changes in human disease risk with the possible expansion of tick populations.

The annual incidence of reported ehrlichiosis and anaplasmosis increased during 2000–2007. The reported incidence of other tick-borne diseases, including Rocky Mountain spotted fever (RMSF) and Lyme disease, also increased during the same period, leading to speculation about possible ecologic or climatic changes resulting in expanding vector or reservoir ranges.[14,29,30] However, numerous other factors likely influenced these observations. These factors include novel diagnostic assays, revised case definitions, increased physician awareness and reporting, and improved state and local surveillance for tick-borne diseases.[30] Specifically, case definition changes in 2000 and 2001 and the publication of national guidelines for the diagnosis of tick-borne rickettsial diseases in 2006 may have broadly increased awareness and case recognition.[16,24,25] During the study period, PCR of whole blood became more widely available as a sensitive and specific tool to aid the early diagnosis of ehrlichiosis and anaplasmosis (Holzbauer S and others, International Conference on Emerging Infectious Diseases, 2010). These changes may have improved reporting of cases through national surveillance systems.

Ehrlichiosis and anaplasmosis contribute substantially to the overall burden of tick-borne rickettsial diseases in the United States. The combined reported incidence rate for ehrlichiosis, anaplasmosis, and UUOA during 2000–2007 was more than 7.2 per million PY, which is similar to the reported incidence of RMSF in recent years.[29] The hospitalization rate was high among reported cases of ehrlichiosis (49%) and anaplasmosis (36%) and was disproportionately greater among the elderly. During 2000–2007 the reported number of fatal outcomes associated with ehrlichiosis and anaplasmosis (n = 43) was similar to that reported for RMSF (n = 35), which has traditionally been considered a disease with a high potential for fatal outcome.[29] Past studies have suggested that infections with *E. chaffeensis* are fatal 3% of the time, and fatal outcomes for infections with *A. phagocytophilum* are less frequently reported.[12,13] Risk factors for severe or fatal outcome include immune compromise and older age: several accounts of ehrlichiosis and anaplasmosis among prior organ allograft recipients have been reported.[31–36] In the current surveillance report, 9 patients reported by CRF had a history of organ transplant, and 239 reported other conditions associated with immune compromise, including cancer, diabetes, and arthritis.

Although not specifically captured as a risk factor in the current surveillance system, at least two anaplasmosis infections transmitted through blood transfusion have been reported, suggesting that blood product recipients are a group at potential risk for infection.[37,38] Finally, delayed administration of doxycycline treatment is a significant risk factor for severe and fatal outcome in tick-borne rickettsial diseases.[39] Although antibiotic administration information was not obtained as part of this study, we expect severe or fatal outcomes among patients for whom doxycycline treatment was initiated early in the course of illness to be rare.

The reported incidence of UUOA was 0.45 cases per million PY, and most cases reported under UUOA were cases of ehrlichiosis or anaplasmosis where the causative species was not differentiated. During the current surveillance period, 70% of UUOA cases were reported from Wisconsin, a state where *A. phagocytophilum* is endemic but *E. chaffeensis* and *E. ewingii* are rarely confirmed. Furthermore, the overall use of the UUOA reporting category in much of the country increased during the studied period. A likely explanation for this increase in use of the category UUOA is physician difficulty in ordering and interpreting appropriate tests to diagnose *A. phagocytophilum*. In 2001, the name human granulocytic ehrlichiosis shifted to human anaplamosis when the organism *Ehrlichia phagocytophila* was renamed *Anaplasma phagocytophilum*.[7,16] We believe this name change led to confusion among healthcare providers about which diagnostic test to request in a given geographic area.

In areas where ehrlichiosis and anaplasmosis are endemic, discerning the etiologic agent requires testing for both. In these geographic areas, cases are ideally reported under UUOA when only a single test is ordered, although the stringency with which this recommendation has been applied during the current study period is not clear. In geographic areas where one agent predominates, lack of testing for the less common agent should not necessarily require a report of UUOA. Further confusing this issue, however, is the fact that a new *Ehrlichia* agent was identified in Wisconsin and Minnesota in 2009 (McFadden JW, International Conference on Emerging Infectious Disease 2010). The new agent appears similar to *E. muris* and may cross-react with assays for *E. chaffeensis* (CDC, unpublished data). The impact of this new agent on national surveillance programs is unknown, and recommended diagnostic testing strategies beyond a differential PCR have not yet been established.

Another factor complicating surveillance for these organisms is cross-reactivity among *E. chaffeensis*, *E. ewingii*, and *A. phagocytophilum* on serologic assays, making it difficult

to interpret the results from inappropriate testing. Wisconsin used the UUOA category to report these poorly defined cases during 2000–2007 (Johnson D, Wisconsin Department of Health, unpublished data). Using an *E. chaffeensis* serologic test to diagnose the cause of illness in a patient residing in an *A. phagocytophilum*-endemic area increases the chance of false-negative results. Serologic cross-reactivity to *E. chaffeensis* can occur in up to half of *A. phagocytophilum* cases.[40] Thus, consistent use of incorrect tests at the provider level will result in a substantial number of missed diagnoses and underestimate the true burden of disease.

Acquisition of appropriate documentation to confirm cases in accordance with the surveillance case definitions remains problematic for rickettsial diseases. Because of its availability and reliability, IFA is considered the gold standard for testing. However, its usefulness is limited unless paired serum samples are tested and an increase in titer (seroconversion) is documented. Patient convalescent-phase samples are not often obtained, yielding at best a probable case definition. In the current study, 2,234 reported ehrlichiosis, anaplasmosis, and UUOA cases (57%) were diagnosed as probable cases using only a single positive serum test result. Because antibodies may remain elevated for months or even years after infection, probable cases represent a group of patients for whom a definitive diagnosis of ehrlichiosis or anaplasmosis is less assured because past exposures can be identified as current cases. Further complicating the validity of a single serum sample is the fact that most cases may lack detectable antibody in the first 7–10 days of illness.[41] Given the continued reliance of physicians in the United States on single serum samples for diagnosis (in this case, most reported cases were diagnosed by using a single serum sample), the true number of ehrlichiosis and anaplasmosis reports is significantly underestimated.

In this report, hospitalized and fatal cases are more likely to be reported as confirmed than less severe cases. We believe cases without a prompt convalescence offer more opportunity and motivation for acquiring diagnostic evidence. Case status lies on the causal pathway between severity of disease and clinical course. Although the variable is designed to capture the strength of supporting laboratory evidence, case status also captures the severity of disease.

Reported incidence rates for ehrlichiosis and anaplasmosis generally increased with age during the study period (Figure 3). Although this finding may reflect the true relationship between age and incidence, this increase may also be the result of an artifact of surveillance. The increasing seropositivity with age may be due to diagnosis of other nonspecific febrile illnesses as tick-borne rickettsial disease among older patients relative to younger patients.[42–44] Conversely, the impact of immune status on the clinical course of illness indicates the importance of host factors, and age may also play an important role in the clinical course.

In this report, almost all cases reporting race and ethnicity were white and non-Hispanic (Table 1). However, a representative cross-sectional study found no association between race and ethnicity with *E. chaffeensis* seropositivity.[44] Because the surveillance case definitions require supporting laboratory evidence, these results may be confounded by access to and use of diagnostic services.[24,45,46] Similarly, missing data and misclassification of race and ethnicity in these surveillance data may significantly bias the results.[47] Because these results relied on passive surveillance methods, the rate estimates presented here represent a minimum incidence. Similarly, these reports relied on patients, physicians, laboratories, State Public Health Departments, and the CDC for accurate reporting, and misclassification and missing data can lead to information bias of an unknown magnitude.

These results summarize the surveillance data reported using the CSTE case definitions during 2000–2007. New case definitions were implemented in 2008 for *E. chaffeensis*, *A. phagocytophilum*, and *E. ewingii* that explicitly name the etiologic agent should help minimize the confusion from prior taxonomic changes.[25] However, surveillance trends may change again in response to these new case criteria. For future iterations of case definitions, specifying stricter requirements on the timing of acute-phase and convalescent-phase serologic analysis for laboratory confirmation of a case would help improve the quality of data obtained. We anticipate continually evolving case definitions will be needed to better define our understanding, recognition, and the reporting of these emerging tick-borne diseases.

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