

## Increasing Incidence of Ehrlichiosis in the United States: A Summary of National Surveillance of *Ehrlichia chaffeensis* and *Ehrlichia ewingii* Infections in the United States, 2008–2012

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**Abstract.** Human ehrlichiosis is a potentially fatal disease caused by *Ehrlichia chaffeensis* and *Ehrlichia ewingii*. Cases of ehrlichiosis are reported to Centers for Disease Control and Prevention through two national surveillance systems: Nationally Notifiable Diseases Surveillance System (NNDSS) and Case Report Forms. During 2008–2012, 4,613 cases of *E. chaffeensis* infections were reported through NNDSS. The incidence rate (IR) was 3.2 cases per million person-years (PYs). The hospitalization rate (HR) was 57% and the case fatality rate (CFR) was 1%. Children aged < 5 years had the highest CFR of 4%. During 2008–2012, 55 cases of *E. ewingii* infection were reported through NNDSS. The national IR was 0.04 cases per million PY. The HR was 77%; no deaths were reported. Immunosuppressive conditions were reported by 26% of cases. The overall rate for ehrlichiosis has increased 4-fold since 2000. Although previous literature suggests *E. ewingii* primarily affects those who are immunocompromised, this report shows most cases occurred among immunocompetent patients. This is the first report to show children aged < 5 years with ehrlichiosis have an increased CFR, relative to older patients. Ongoing surveillance and reporting of tick-borne diseases are critical to inform public health practice and guide disease treatment and prevention efforts.

### INTRODUCTION

Human ehrlichioses are potentially fatal tick-borne infections caused by the obligate intracellular bacterium of the *Ehrlichia* genus, including *Ehrlichia chaffeensis* and *Ehrlichia ewingii*. The first reported case of human monocytic ehrlichiosis (HME) caused by *E. chaffeensis* was documented in 1991.<sup>1</sup> *Ehrlichia ewingii* was first identified as the etiologic agent of canine granulocytic ehrlichiosis in 1992 and as one of the etiologic agents of human ehrlichiosis in 1999.<sup>2,3</sup> The majority of reported human ehrlichiosis cases are caused by *E. chaffeensis*, which is the most frequently diagnosed tick-borne disease in the southern United States.<sup>4,5</sup> Human ehrlichiosis caused by *E. ewingii* is less commonly reported and most infections have historically occurred among immunocompromised patients.<sup>2,6–9</sup>

Symptoms of ehrlichiosis are nonspecific and typically begin within 7–14 days of exposure.<sup>6</sup> Patients are most likely to seek medical attention approximately 3 days after onset of symptoms.<sup>6,9–11</sup> Presenting clinical features most often include fever, chills, headache, malaise, myalgia, and nausea.<sup>2,6</sup> Fewer than 30% of adult patients and 60% of children infected with *E. chaffeensis* have a rash, which is maculopapular in early stages and can be petechial in late stages.<sup>4,6,9,10,12</sup> Rash typically appears on the trunk around 7 days after onset of illness, and often spares the hands and feet.<sup>9,13</sup> In *E. ewingii* cases, rash is rare.<sup>9</sup> Leukopenia, thrombocytopenia, and elevations in serum hepatic aminotransferase levels are frequent laboratory findings.<sup>6</sup> Severe illness may include cough, diarrhea, confusion, and lymphadenopathy in adults; and edema of the hands or feet in children.<sup>6</sup> When left untreated or when treatment is delayed, severe complications may occur and include adult respiratory distress syndrome (ARDS), a disseminated intravascular coagulation-like syndrome (DIC), central nervous system involvement, and renal failure.<sup>6,14</sup> Ehrlichiosis generally manifests as a moderate to severe illness, and 50–70% of patients are hospitalized.<sup>9–11</sup> In *E. chaffeensis* infections, death

can occur as early as the second week of illness and has been reported in 1–3% of cases.<sup>9,10</sup> Infection by *E. ewingii* usually results in milder illness compared with *E. chaffeensis*, and no *E. ewingii* deaths have been reported.<sup>6,10</sup> Patients with ehrlichiosis and who are immunocompromised, especially from human immunodeficiency virus (HIV), cancer treatments, or organ transplants, are at highest risk for severe outcome.<sup>8,15–23</sup> As recommended by the American Academy of Pediatrics (AAP) and the Centers for Disease Control and Prevention (CDC), doxycycline, a tetracycline-class antibiotic, is the treatment of choice for children and adults of all ages with rickettsial disease, including ehrlichiosis; treatment should never be withheld pending laboratory confirmation.<sup>9,13,24</sup> Treatment with doxycycline within the first 5 days of illness has been shown to decrease severity of disease in patients when compared with patients who were treated later in the course of illness.<sup>11,13</sup>

The primary vector for *E. chaffeensis* and *E. ewingii* in the United States is the lone star tick, *Amblyomma americanum*.<sup>25,26</sup> Transmission to humans is caused almost exclusively by the bites of infected ticks and occurs in areas where the lone star tick is prevalent, most commonly in the southeastern, southcentral, and, recently, northeastern United States.<sup>4,5,10,27</sup> Lone star ticks are aggressive, nonspecific feeders, which bite humans at all stages of their life cycle.<sup>25</sup> The feeding cycle of the lone star tick coincides with the seasonality of ehrlichiosis, particularly the nymphal and adult stages, which transmit the bacteria, with cases peaking from May through July.<sup>4,6,10</sup> White-tailed deer (*Odocoileus virginianus*), which are naturally infected with *E. chaffeensis*, maintain the enzootic cycle of *E. chaffeensis*.<sup>25,28,29</sup> In addition, canids, domestic dogs, goats, rabbits, red foxes, raccoons, opossums, rodents, birds, and wild turkeys can serve as hosts for the lone star tick; though few mammals or birds are exempt as potential hosts.<sup>10,25,28</sup> In addition, dogs may serve as transport hosts by carrying infected ticks in closer proximity to humans in households; this can lead to establishment of a focus of infection at or near the residence.<sup>10,25</sup> *Ehrlichia ewingii* is maintained in a similar enzootic cycle, with white-tailed deer and domestic dogs serving as reservoir species.<sup>5,29</sup> Transmission of *E. chaffeensis* through transplants and transfusions, such as of the liver and kidneys, has also been reported.<sup>6,10,13,18,30</sup>

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Similarly, a case of *E. ewingii* in an immunocompromised young boy transmitted through a platelet transfusion has been reported.<sup>17</sup>

Ehrlichiosis has been a nationally notifiable disease since 1999.<sup>31</sup> In 2008, the Council of State and Territorial Epidemiologists (CSTE) case definition changed to differentiate between ehrlichiosis and anaplasmosis, and to include the following categories for ehrlichiosis: *E. chaffeensis* infection (formerly HME); *E. ewingii* infection (formerly ehrlichiosis [unspecified, or other agent]); and ehrlichiosis/anaplasmosis, human, undetermined. Presented here is a summary of passive surveillance of *E. chaffeensis* and *E. ewingii* infections in the United States with onset dates during 2008–2012.

## MATERIALS AND METHODS

**National surveillance systems.** Individual state and territory health departments report surveillance data to CDC through the Nationally Notifiable Diseases Surveillance System (NNDSS) and through manually completed Tick-Borne Rickettsial Disease Case Report Forms (CRFs) ([http://www.cdc.gov/ticks/forms/2010\\_tbrd\\_crf.pdf](http://www.cdc.gov/ticks/forms/2010_tbrd_crf.pdf)). Demographic data, including county and state of residence, sex, ethnicity, and race, are reported through NNDSS. Cases are reported as probable or confirmed by the state and local health departments. Data reported through CRFs includes county and state of residence, clinical course, immunosuppressive conditions, hospitalization status, laboratory results, and patient outcome.

**Case definition.**<sup>31</sup> To meet the confirmed case definition, a case must meet both clinical and laboratory criteria. Clinical presentation must include fever and one or more of the following symptoms: headache, myalgia, anemia, leukopenia, thrombocytopenia, or any hepatic transaminase elevation. Laboratory criteria for a confirmed case of *E. chaffeensis* infection includes demonstration of one of the following: a 4-fold change in immunoglobulin G (IgG)-specific antibody titer against *E. chaffeensis* antigen by indirect immunofluorescence antibody assay (IFA) between paired serum samples (one taken in first week of illness and a second 2–4 weeks later); detection of *E. chaffeensis* DNA in a clinical specimen via polymerase chain reaction (PCR) assay; demonstration of *E. chaffeensis* antigen in a biopsy or autopsy sample by immunohistochemical methods; or isolation of *E. chaffeensis* from a clinical specimen in cell culture. To meet the probable case definition for *E. chaffeensis* infection, the clinical criteria must be met and one of the following should be met for laboratory evidence: serological evidence of elevation of IgG or IgM antibody reactive with *E. chaffeensis* antigen by IFA, enzyme-linked immunosorbent assay (ELISA), dot-ELISA, or assays in other formats, or identification of morulae in the cytoplasm of monocytes or macrophages by microscopic examination. Because *E. ewingii* had not been cultured during 2008–2012, antigen was not available; thus, *E. ewingii* infections could only be diagnosed by PCR. The CSTE case definition is applied by CDC to data provided on CRFs.

**Analysis.** Confirmed and probable cases of ehrlichiosis reported to CDC through both surveillance systems from January 2008 through December 2012 were included in this analysis. When date of onset of symptoms was not reported, the earliest known date associated with the case was used as a proxy. The year of symptom onset instead of reporting

year was used for analyses; therefore, the number of cases presented here may differ from reports of the annual number of cases published in Morbidity and Mortality Weekly Report annual summaries. Data from NNDSS were used to calculate incidence rates (IRs) by year, state, and age. IRs were calculated as the number of ehrlichiosis cases per million person-years (PYs) using U.S. Census Bureau population estimates.<sup>32,33</sup> Because of a large proportion of cases with missing data, IRs were not reported for race and ethnic groups. Ehrlichiosis caused by *E. chaffeensis* was not considered a notifiable disease during some years in Iowa (2008–2012), North Dakota (2008–2010), District of Columbia (2008–2012), Colorado (2008–2012), Idaho (2008–2012), Montana (2008–2012), Nevada (2008–2010), New Mexico (2008–2012), Alaska (2008–2012), Hawaii (2008–2012), and Washington (2008–2009). Ehrlichiosis caused by *E. ewingii* was not considered a notifiable disease during some years in Iowa (2008–2012), Nebraska (2008–2010), North Dakota (2008–2010), District of Columbia (2008–2012), Colorado (2008–2012), Idaho (2008–2012), Montana (2008–2012), Nevada (2008–2009), New Mexico (2008–2012), Alaska (2008–2012), Hawaii (2008–2012), and Washington (2008–2009). State populations were only considered at risk in years in which ehrlichiosis was reportable. CRFs are received by CDC on a rolling basis; therefore, only CRFs received before March 10, 2015 were included in this analysis. Confirmed and probable CRFs were used to calculate hospitalization and case fatality rates (CFRs), laboratory diagnostic test usage, seasonality, and severe complications related to ehrlichiosis. Reports missing these data were excluded from that segment of the analysis. Data analysis was performed using SAS v9.3 software (SAS Institute, Cary, NC). Because these reported cases are not generalizable to unreported cases or to other reporting time periods, we do not present confidence intervals or results from statistical hypotheses testing.

## RESULTS

**Ehrlichia chaffeensis. NNDSS data.** Through NNDSS, a total of 4,613 cases of *E. chaffeensis* were reported with an illness onset date between 2008 and 2012; 1,461 (32%) were reported as confirmed cases (Table 1). The percent of cases meeting a confirmed case definition increased during the study period from 24% in 2008 to 39% in 2012. The national reported IR was 3.2 cases per million PY (Figure 1). States with the highest reported IRs include: Oklahoma (30.9), Missouri (26.3), Delaware (19.8), Arkansas (19.4), Virginia (10.8), and Tennessee (9.7) (Table 2 and Figure 2). These six states accounted for 54% of all reported cases of human ehrlichiosis caused by *E. chaffeensis* in the United States.

More males (57%) than females were reported with *E. chaffeensis* infection through NNDSS (Table 1). Of those reporting race, cases were primarily among whites (64%), followed by blacks (3%), and American Indians (3%). Hispanic ethnicity was reported for 2% of cases. The overall mean and median age of onset was 51 and 55 years of age, respectively. The reported IR increased with age, and the rate among persons 65–69 years of age (7.9) was the highest when compared with the entire population (Figure 3).

Reported symptom onset dates peaked in the summer months from May through July ( $N = 2,972$ , 64%); the fewest

TABLE 1

Demographic profiles and case classification for *Ehrlichia chaffeensis* and *Ehrlichia ewingii* as reported to the Nationally Notifiable Diseases Surveillance System (NNDSS) and Case Report Forms (CRFs), United States, 2008–2012

	NNDSS		CRFs	
	<i>E. chaffeensis</i>	<i>E. ewingii</i>	<i>E. chaffeensis</i>	<i>E. ewingii</i>
	N = 4,613, no. (%)	N = 55, no. (%)	N = 3,593, no. (%)	N = 54, no. (%)
<b>Case classification</b>				
Confirmed	1,461 (31.7)	55 (100)	993 (28.1)	54 (100)
Probable	3,147 (68.2)		2,546 (71.9)	
Unknown*	5 (0.1)			
<b>Sex</b>				
Male	2,606 (56.5)	28 (50.9)	2,070 (58.5)	28 (51.9)
Female	1,872 (40.6)	24 (43.6)	1,430 (40.4)	26 (48.1)
Unknown	135 (3.0)	3 (5.5)	39 (1.1)	0 (0)
<b>Race</b>				
White	2,959 (64.1)	35 (63.6)	2,554 (72.1)	42 (77.8)
Black	134 (2.9)	2 (3.6)	87 (2.4)	1 (1.9)
American Indian†	132 (2.9)	0 (0)	129 (3.6)	0 (0)
Asian‡	18 (0.4)	0 (0)	14 (0.4)	0 (0)
Unknown	1,370 (29.7)	18 (32.7)	755 (21.0)	11 (20.4)
<b>Ethnicity</b>				
Hispanic	90 (2.0)	0 (0)	57 (1.6)	0 (0)
Non-Hispanic	2,723 (59.7)	37 (67.3)	2,269 (63.2)	37 (68.5)
Unknown	1,750 (38.4)	18 (32.7)	1,209 (33.6)	17 (31.5)
<b>Age (years)</b>				
< 5	82 (1.8)	0 (0)	69 (1.9)	0 (0)
5–9	132 (2.9)	1 (1.8)	100 (2.9)	1 (1.9)
10–14	123 (2.7)	0 (0)	102 (2.8)	0 (0)
15–19	165 (3.6)	0 (0)	122 (3.4)	0 (0)
20–24	138 (3.0)	1 (1.8)	107 (3.0)	1 (1.9)
25–29	114 (2.5)	3 (5.5)	86 (2.4)	3 (5.6)
30–34	196 (4.3)	0 (0)	145 (4.0)	0 (0)
35–39	230 (5.0)	4 (7.3)	157 (4.4)	4 (7.4)
40–44	269 (5.8)	4 (7.3)	192 (5.3)	4 (7.4)
45–49	391 (8.5)	5 (9.1)	279 (7.8)	4 (7.4)
50–54	408 (8.8)	4 (7.3)	312 (8.7)	4 (7.4)
55–59	510 (11.1)	8 (14.6)	382 (10.6)	9 (16.7)
60–64	502 (11.0)	6 (10.9)	401 (11.2)	4 (7.4)
65–69	467 (10.1)	6 (10.9)	361 (10.0)	8 (14.8)
70+	853 (18.5)	13 (23.6)	637 (17.7)	11 (20.4)
Unknown	31 (0.7)	0 (0)	87 (2.4)	1 (1.9)

\* California.

† Or Alaskan native.

‡ Or Pacific Islander.

cases were reported during the winter months of December, January, and February ( $N = 146$ , 3%) (Figure 4).

**CRF data.** During the same study period, 3,593 cases of *E. chaffeensis* were reported to CDC via CRFs. Cases reported through CRFs were similar to NNDSS cases in terms of confirmed cases (28%), gender (59% male), age (mean age 51 years and median age 55 years), and race distribution (72% white, 4% American Indian, and 3% black) (Table 1). The percent of confirmed cases reported through CRFs also increased during the study period from 20% in 2008 to 37% in 2012.

Among cases reporting hospitalization status, 1,584 (57%) were hospitalized during the course of illness. There was a higher hospitalization rate among confirmed cases (77%) than probable cases (48%). More males (60%) were hospitalized than females (54%). A higher proportion of cases was hospitalized among persons over 60 than among other age groups. For those reporting race and hospitalization status, blacks were most frequently hospitalized (75%), followed by Asian/Pacific Islanders (60%) and whites (59%). Of

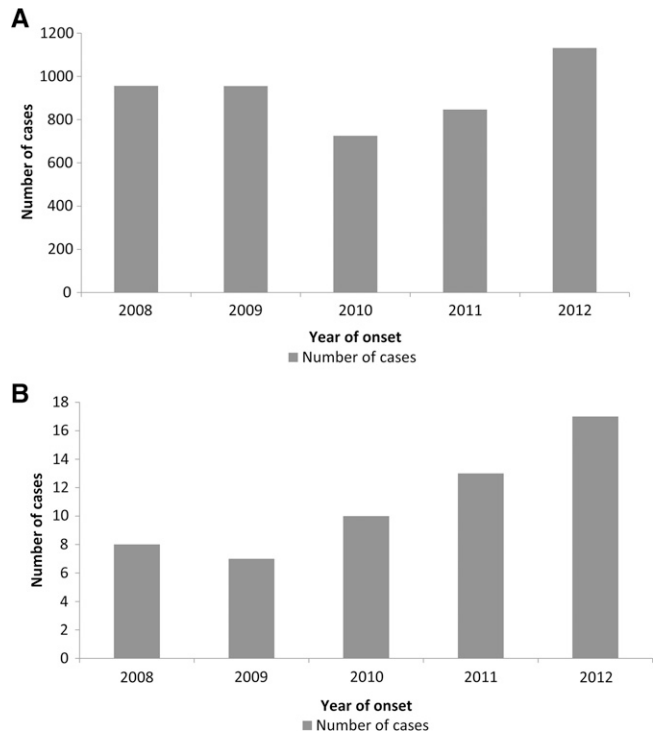


FIGURE 1. Number of annual cases vs. the year of onset of symptoms, 2008–2012, for (A) *Ehrlichia chaffeensis* infections and (B) *Ehrlichia ewingii* infections in the United States. The number of incident cases is from the Nationally Notifiable Diseases Surveillance System.

those reporting the presence of life-threatening complication, 399 cases were (11%) reported suffering from a life-threatening complication. These complications included renal failure (8%), meningitis (5%), ARDS (3%), DIC (2%), pneumonia (1%), and sepsis (1%).

Of those reporting clinical outcome, there were 29 (1%) fatal cases. Confirmed cases had a higher percentage of patients with fatal outcome (2%) compared with probable cases (0.6%). The annual CFR remained consistent throughout the study period (range = 0.7–1%). Of those reporting race and fatal outcome, American Indians, blacks, and whites experienced the highest reported CFR (1%). CFRs were highest among children < 5 years of age (4%) and persons  $\geq 70$  years of age (3%) than among other age groups (Figure 5). Among confirmed cases, the CFR among children < 5 years of age increases to 14% and the CFR among persons  $\geq 70$  increases to 53%.

Among those reporting immune status ( $N = 2,319$ ), 327 cases (14%) reported immunosuppressive conditions. These conditions included diabetes (3%), cancer (2%), history of organ transplant (1%), asplenia (0.5%), hepatitis C (0.5%), and HIV (0.4%). The median age of those with an immunosuppressive condition was 60 years, and the median age among immunocompetent persons was 55 years. When compared with immunocompetent case outcomes, risk for severe outcome for immunosuppressed cases was higher for hospitalization (relative risk [RR] = 1.4), presence of life-threatening complication (RR = 2.4), and death (RR = 2.3).

Most cases of infection with *E. chaffeensis* were diagnosed using IFA specific for IgG ( $N = 2,240$ , 63%). However, only a small number of these serologic diagnoses ( $N = 112$ , 3%)

TABLE 2

The number of reported cases and the reported incidence rate (IR) per million person-years by state for *Ehrlichia chaffeensis* and *Ehrlichia ewingii*, 2008–2012

State	<i>E. chaffeensis</i>	<i>E. ewingii</i>
	No. of cases (rate*)	No. of cases (rate*)
Alabama	45 (1.9)	0 (0)
Alaska	NN	NN
Arizona	0 (0)	0 (0)
Arkansas	283 (19.4)	0 (0)
California	5 (0.03)	0 (0)
Colorado	NN	NN
Connecticut	2 (0.1)	0 (0)
Delaware	89 (19.8)	5 (1.1)
District of Columbia	NN	NN
Florida	69 (0.7)	0 (0)
Georgia	104 (2.1)	1 (0.02)
Hawaii	NN	NN
Idaho	NN	NN
Illinois	138 (2.2)	1 (0.02)
Indiana	4 (0.1)	0 (0)
Iowa	NN	NN
Kansas	71 (5)	1 (0.1)
Kentucky	87 (4)	0 (0)
Louisiana	2 (0.1)	1 (0.04)
Maine	10 (1.5)	0 (0)
Maryland	183 (6.3)	2 (0.1)
Massachusetts	55 (1.7)	0 (0)
Michigan	18 (0.4)	0 (0)
Minnesota	50 (1.9)	2 (0.1)
Mississippi	14 (0.9)	0 (0)
Missouri	788 (26.3)	33 (1.1)
Montana	NN	NN
Nebraska	8 (0.9)	0 (0)
Nevada	0 (0)	0 (0)
New Hampshire	18 (2.7)	0 (0)
New Jersey	326 (7.4)	0 (0)
New Mexico	NN	NN
New York City	35 (0.9)	0 (0)
New York State	250 (4.5)	0 (0)
North Carolina	374 (7.8)	0 (0)
North Dakota	0 (0)	0 (0)
Ohio	40 (0.7)	1 (0.02)
Oklahoma	580 (30.9)	0 (0)
Oregon	0 (0)	0 (0)
Pennsylvania	27 (0.4)	0 (0)
Rhode Island	43 (8.2)	0 (0)
South Carolina	12 (0.5)	1 (0.04)
South Dakota	1 (0.2)	0 (0)
Tennessee	309 (9.7)	5 (0.2)
Texas	43 (0.3)	0 (0)
Utah	0 (0)	0 (0)
Vermont	1 (0.3)	0 (0)
Virginia	432 (10.8)	2 (0.05)
Washington	1 (0.05)	0 (0)
West Virginia	5 (0.5)	0 (0)
Wisconsin	91 (3.2)	0 (0)
Wyoming	0 (0)	0 (0)

The number of incident cases is from the Nationally Notifiable Diseases Surveillance System and the number of person-years at risk is from the U.S. Census Bureau, 2008–2012. States where the disease was not notifiable for the duration of 2008–2012 are designated as “NN.”  
\*IR per million persons per year.

demonstrated seroconversion and were reported as confirmed cases. A single positive, acute-phase serologic result was the only supporting laboratory evidence for 2,126 cases (60%). Among probable cases reporting positive IgG or IgM titers, onset date, and serology collection date, the median number of days from onset date to date of first serology collection date was 7 days (interquartile range [IQR] = 2–14). A total of 935 cases (26%) were confirmed by PCR. The

proportion of cases confirmed by PCR increased from less than 20% during 2008–2009 to 35% in 2012 (Figure 6). Of all confirmed cases ( $N = 1,047$ , 30%), most (89%) were confirmed by PCR. Among confirmed cases reporting positive PCR or culture results, onset date, and serology collection date, the median number of days from onset date to date of first serology collection date was 5.5 days (IQR = 3–9).

***Ehrlichia ewingii*. NNDSS data.** Through NNDSS, 55 cases of *E. ewingii* infection were reported with an onset date between 2008 and 2012. All cases were confirmed by PCR ( $N = 55$ ), as required to meet the case definition. The national reported IR was 0.04 cases per million PY. During the study period, reported IR increased from 0.03 cases per million PY in 2008 to 0.06 cases per million PY in 2012 (Figure 1). States with the highest reported IRs were Delaware (1.1) and Missouri (1.1) (Table 2). These two states accounted for 69% of all *E. ewingii* cases reported in the United States.

Slightly more males (51%) than females were reported with *E. ewingii* infection through NNDSS (Table 1). Among those reporting race, cases were primarily among persons of white race (64%). The overall mean and median ages were 56 and 58 years, respectively. Reported IR increased with age, and rates among persons over 65 years of age (0.1) were the highest when compared with the national average (Figure 3).

Reported symptom onset dates peaked in the summer months from June through August ( $N = 47$ , 85%), with fewer cases reported during the fall months of September and October ( $N = 2$ , 4%) (Figure 4). No cases were reported in January, February, March, November, or December.

**CRFs data.** During the same study period, 54 cases of *E. ewingii* were reported to CDC via CRFs. The cases reported through CRFs were similar to NNDSS cases in terms of gender (52%), age (mean age: 55.6 years and median age: 58 years), and race distribution (78% white and 2% black) (Table 1). As written in the case definition, all cases were confirmed by PCR ( $N = 54$ ).

Among cases reporting hospitalization status ( $N = 52$ ), 40 (77%) were hospitalized during the course of illness. More females (79%) were hospitalized than males (75%). There was one case (2%) for which a specific life-threatening complication (renal failure) was reported. Of the cases reporting clinical outcome ( $N = 52$ ), there were no fatalities. Among those reporting immune status ( $N = 38$ ), 10 cases (26%) reported immunosuppressive conditions, including five cases (13%) with history of organ transplantation and three cases (8%) with history of cancer. There were no cases reporting HIV infection. The median age of those with an immunosuppressive condition was 65.5 years and the median age among immunocompetent persons was 58.5 years. Cases reported for patients having an immunosuppressive condition were more likely to be hospitalized (RR = 1.6) than for those who were immunocompetent.

## DISCUSSION

The IR for ehrlichiosis has continued to increase since becoming a nationally notifiable disease in 1999. In our previous report, the incidence of ehrlichiosis caused by *E. chaffeensis* was 1.4 cases per million PY during 2000–2007.<sup>14</sup>

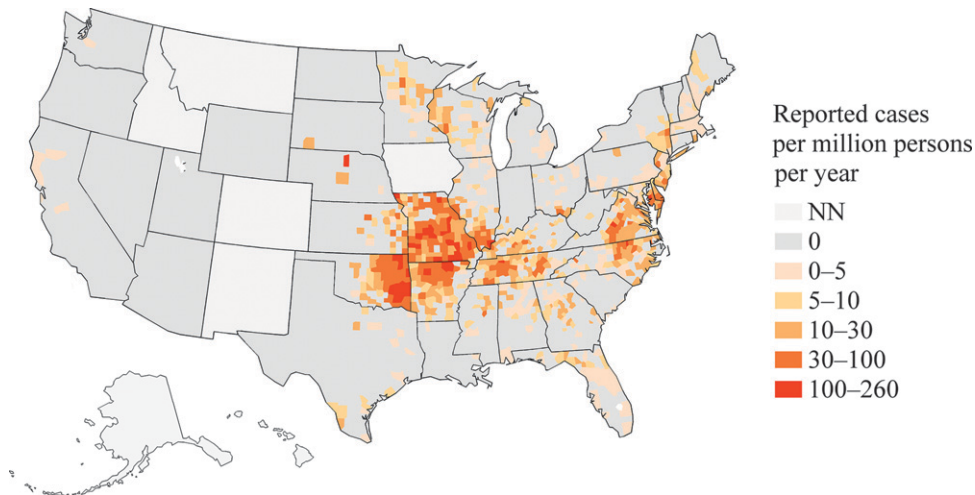


FIGURE 2. A map of incidence rates determined from reported *Ehrlichia chaffeensis* infections in the counties in the United States, 2008–2012. States where the disease was not notifiable for the duration of 2008–2012 are shaded with the “NN” category. The number of incidence cases is from the Nationally Notifiable Diseases Surveillance System, and the number of person-years at risk is from the U.S. Census Bureau.

In this report, the incidence of ehrlichiosis caused by *E. chaffeensis* more than doubled to 3.2 cases per million PY during 2008–2012. This is the first report to show children aged < 5 years with ehrlichiosis may have an increased CFR relative to older patients. Additionally, this is the first report to summarize the reported epidemiology of *E. ewingii* infections in the United States.

Previous case reports suggested *E. ewingii* primarily affects those who are immunocompromised, which may be because immunocompromised persons are more likely to develop serious infections, be hospitalized, and have extensive laboratory diagnostic tests.<sup>2,7,8,15,17,34</sup> In addition, because *E. ewingii* is a milder illness, it is possible that immunocompetent patients may have less severe symptoms and not seek medical attention, which may have led to overrepresentation of immunocompromised cases in previous reports. In our report, the prevalence of reporting an immunosuppressive condition was 26% among *E. ewingii* cases; cases with *E. ewingii* infections reporting an immunocompromised condition were more likely to be hospitalized. Of the 985 PCR-positive reports of *Ehrlichia* species infections reported through CRFs, 54 were positive for *E. ewingii*; increased availability and utilization of species-specific PCR assays may further elucidate the epidemiology of *E. ewingii* infections in the United States.

The diagnostic laboratory gold standard for confirming *E. chaffeensis* infection is seroconversion: a 4-fold titer increase when comparing an acute and convalescent serum using an IFA specific for IgG.<sup>9,14</sup> Here, only 112 (3%) cases were reported as confirmed with paired sera. During the first week, IFA is often negative.<sup>10</sup> Since most patients develop diagnostic IFA titers by 4 weeks after illness onset, it is important to obtain a convalescent-phase serum sample, as this may be the only laboratory evidence to support the diagnosis.<sup>9,14</sup> However, convalescent samples are often not obtained or provided to the diagnostic laboratory. Another caveat of serologic testing is that because *Ehrlichia* spp. and *Anaplasma phagocytophilum* are antigenically related, serologic assays may be positive for more than one agent and results must be interpreted with consideration of epidemiological and clinical findings.<sup>2,5,6,10</sup> PCR on whole blood collected during acute ill-

ness may provide early laboratory evidence of infection with an *Ehrlichia* species, and, unlike serologic methods, PCR can differentiate between *Ehrlichia* species and can provide confirmation from a single acute specimen.<sup>6,8</sup> Therefore, PCR on acute specimens is an effective and efficient method for providing laboratory evidence of ehrlichiosis. During 2000–2007, 11% of cases were confirmed by PCR, whereas 26% of cases were confirmed by PCR during 2008–2012.<sup>14</sup> Without PCR confirmation, it is likely that cases of ehrlichiosis will be missed, and *E. chaffeensis*, *E. ewingii*, and *Anaplasma* infections will be misclassified based on serologic test results. When ehrlichiosis is suspected, PCR testing should be requested in addition to paired-IFA IgG serology for completeness.

The results presented here are subject to several limitations. Persons with poor access to care and diagnostic services may be underrepresented in these data because of the requirement for laboratory evidence for reported cases. Unfortunately, many persons infected with *E. ewingii* and other *Ehrlichia* and *Anaplasma* agents (e.g., *Ehrlichia muris-like agent* [EMLA], *A. phagocytophilum*) also produce antibodies reactive with *E. chaffeensis*.<sup>35–37</sup> Recently, researchers tested 75,077 samples from patients in the United States and found 69 samples were PCR positive for EMLA; samples from patients from Minnesota and Wisconsin made up 93% of the positive samples, which may account for some of the probable reported cases of *E. chaffeensis* infection from Minnesota and Wisconsin.<sup>35</sup> Thus, probable cases of ehrlichiosis may not have been caused by *E. chaffeensis*; without PCR testing, the species cannot be determined for acute probable infections. Studies have shown age is a predictor of prevalence of IFA antibodies to *Ehrlichia* among healthy children and adults; a titer meeting the cutoff for a probable case may be found in persons with previous *Ehrlichia* infections.<sup>37–39</sup> The increasing rates of incidence and hospitalization with age may reflect background seroprevalence and/or there is an age-dependent severity of illness leading to hospitalization and an accurate diagnosis. Due to limitations of our data, we are unable to estimate the number of reported cases because of seroprevalence from previous infections. This question warrants further research; enhanced surveillance

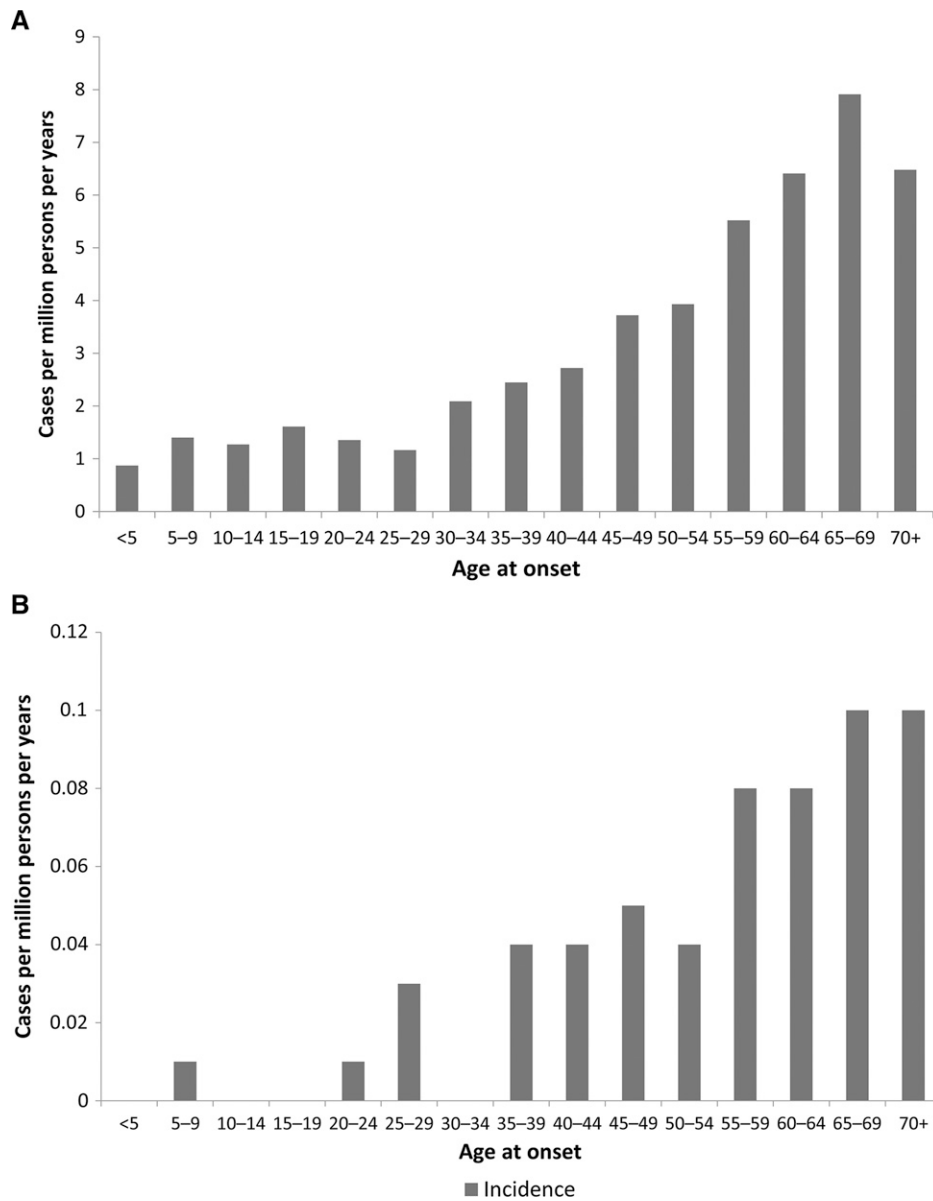


FIGURE 3. Incidence rates (IRs) by age group of (A) *Ehrlichia chaffeensis* and (B) *Ehrlichia ewingii* based on cases reported through the National Notifiable Diseases Surveillance System, United States, 2008–2012. IRs are cases per million person-years.

in highly endemic areas may provide further insight. In addition, cases may be underestimated because of asymptomatic infections or mild illnesses, especially for *E. ewingii* infections, not prompting medical consultation or treatment.<sup>11,37,40</sup> Cases reported here probably represent those of more serious illness and those from highly endemic areas. Clinical suspicion for ehrlichiosis may be lower in nonendemic areas, which will also lead to underreporting. Data for race and ethnicity were largely missing in both NNDSS and CRFs datasets, making it difficult to draw conclusions on the potential role of race and ethnicity related to infections. When measuring the rates of life-threatening complications (e.g., DIC, ARDS, etc.), we are limited to data provided on CRFs and do not receive patient symptoms or laboratory data related to these complications. Finally, results from passive surveillance are not generalizable to the whole population and likely underestimate the true burden of disease.

Ehrlichiosis and Rocky Mountain spotted fever (RMSF) have similar geographic distributions and early clinical presentations.<sup>41</sup> Both the AAP and the CDC recommend treating suspected ehrlichiosis and RMSF with doxycycline, a tetracycline-class antibiotic. Studies from the 1960s indicated that tetracycline causes a characteristic staining of children's developing teeth.<sup>42,43</sup> Doxycycline is a newer tetracycline-class antibiotic, which binds less readily to calcium, and no reports have linked doxycycline to staining of a child's developing permanent teeth, despite several investigations looking for this association.<sup>24,44,45</sup> The current doxycycline label indicates unless there are no other effective antibiotics, this drug should be avoided in children under 8 years old to avoid staining of permanent teeth.<sup>46</sup> The label does not address that there are no equally effective alternatives for the treatment of rickettsial disease, or that short courses of doxycycline have not been shown to have this

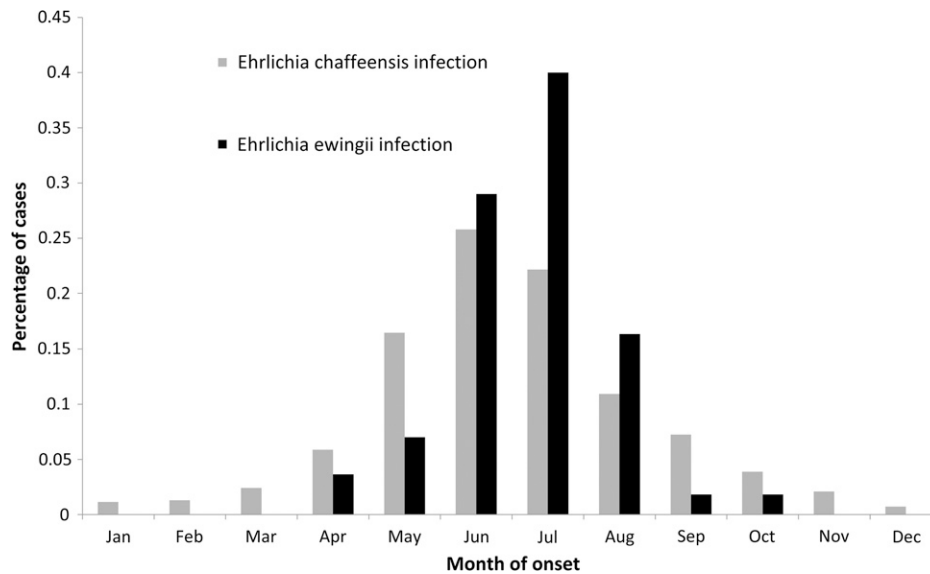


FIGURE 4. Percentage of cases by month of onset for *Ehrlichia chaffeensis* ( $N = 4,563$ ) and *Ehrlichia ewingii* ( $N = 53$ ) infections based on cases reported through the Nationally Notifiable Diseases Surveillance System, United States, 2008–2012.

effect.<sup>44,46</sup> Recent surveys suggest health-care providers may be less willing to prescribe doxycycline for suspected cases of RMSF in children less than 8 years old when compared with older children and adults.<sup>46,47</sup> It is possible that some health-care providers are hesitant to prescribe doxycycline to children with suspected rickettsial disease over concerns about possible dental staining. A gap between the recommendations for treating suspected ehrlichiosis and practice may explain part of the increased CFR among children under 5 years old. It is critical to increase awareness among health-care providers that the empiric treatment of patients with

doxycycline is essential as soon as a tick-borne rickettsial disease is suspected.

While the timely and appropriate treatment of patients with doxycycline can save lives, the best prevention approach for human ehrlichiosis is avoiding tick bites. Tick checks should be performed regularly on people and pets, especially after returning from possible tick-infested areas. Other prevention techniques for humans primarily involve restricting exposure to ticks by wearing personal protection, such as full-coverage clothing treated with permethrin and use of repellants containing *n,n*-diethyl-*m*-toluamide (DEET). There is no vaccine

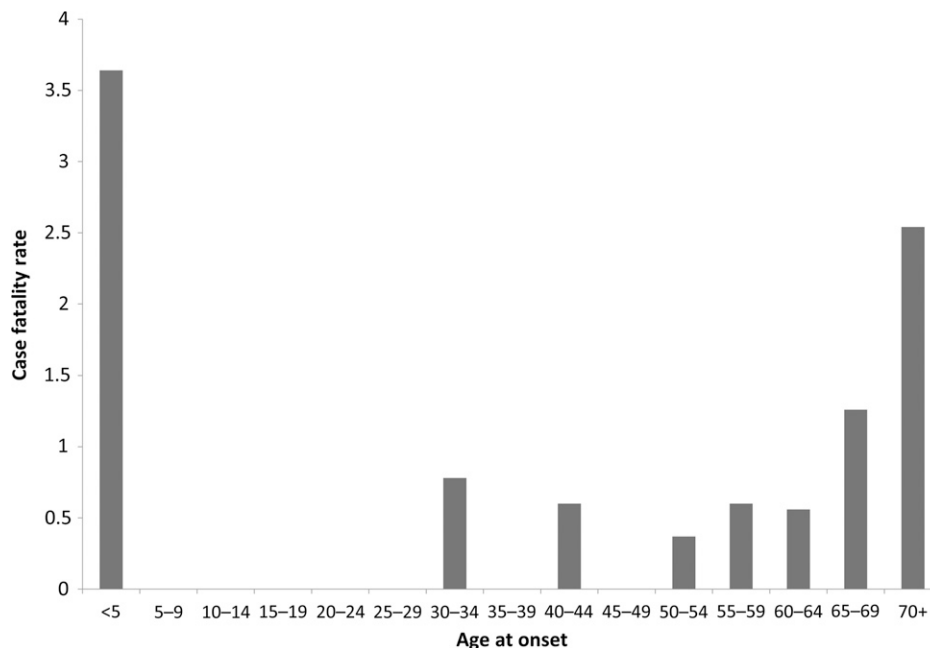


FIGURE 5. Case fatality rate by age group of *Ehrlichia chaffeensis* infection based on cases reported through Case Report Forms, United States, 2008–2012.

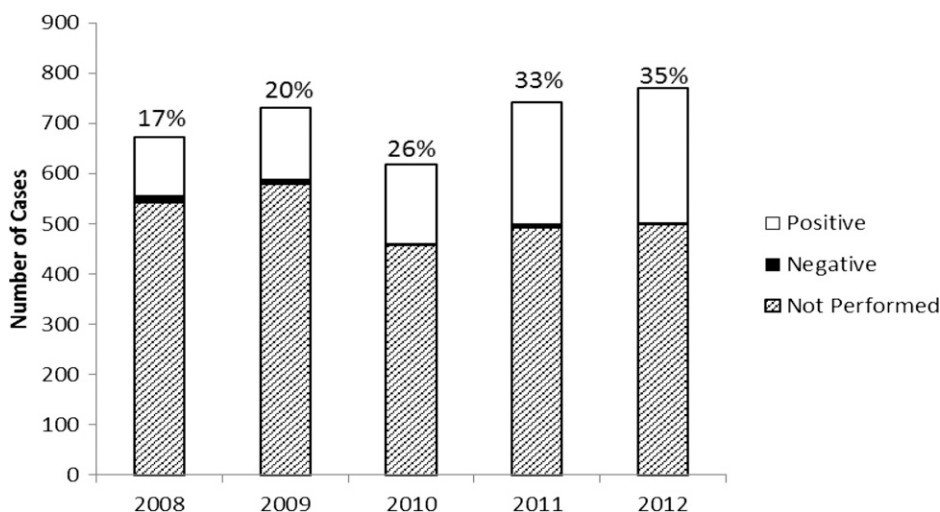


FIGURE 6. Summary of the number of annual cases of *Ehrlichia chaffeensis* ( $N = 3,593$ ), reported through Case Report Forms, United States, 2008–2012. The annual number of cases is subdivided into polymerase chain reaction (PCR)-positive cases, PCR-negative cases, and cases for which PCR was not performed. The annotation above each vertical bar indicates the annual percent of reported cases diagnosed by PCR.

and currently no evidence suggesting post-tick bite prophylaxis is effective for prevention of ehrlichiosis.<sup>9,13,48</sup> Reducing rates of human infection often hinges on effective control of vectors or reservoir populations.<sup>25</sup> Since dogs can be transport hosts for some ticks that carry *Ehrlichia* species and dogs are also considered a reservoir for *E. ewingii*, pet owners should use veterinary ectoparasite controls, such as acaricide-impregnated collars or topical treatments, to prevent ticks from attaching to and feeding on pets.

The increasing incidence and geographic distribution of human ehrlichiosis suggests that health-care providers in previously unaffected areas may begin to see patients present with ehrlichiosis; and, state and local public health departments may begin receiving the first positive laboratory results for ehrlichiosis—both *E. chaffeensis* and *E. ewingii*—among residents with no history of travel. As ehrlichiosis continues to spread geographically, more states might consider making ehrlichiosis a notifiable condition. Ongoing surveillance and reporting of tick-borne diseases are critical for understanding the changing epidemiology of ehrlichiosis, for developing effective prevention strategies and public health education programs, and to inform public health practice and guide disease prevention efforts.

Received July 23, 2015. Accepted for publication October 1, 2015.

Published online November 30, 2015.

**Acknowledgments:** We kindly thank the health-care providers, laboratorians, and public health partners whose dedication and work is indispensable to rickettsial disease surveillance. We also thank Eric Mandel, John Krebs, and Jennifer McQuiston for their work in designing and building these data.

**Disclaimer:** The author was supported in part by an appointment to the Research Participation Program at the Centers for Disease Control and Prevention administered by the Oak Ridge Institute for Science and Education through an interagency agreement between the U.S. Department of Energy and CDC. The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention. All authors report no potential conflicts of interest.

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