Undetermined Human Ehrlichiosis and Anaplasmosis in the United States, 2008–2012: A Catch-All for Passive Surveillance

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Abstract. Human ehrlichiosis and anaplasmosis are potentially severe illnesses endemic in the United States. Several bacterial agents are known causes of these diseases: *Ehrlichia chaffeensis*, *Ehrlichia ewingii*, *Ehrlichia muris*-like agent, Panola Mountain *Ehrlichia* species, and *Anaplasma phagocytophilum*. Because more than one agent may be present in one area, cases of human ehrlichiosis and anaplasmosis may be reported as “human ehrlichiosis/anaplasmosis undetermined” when the available evidence does not suggest an etiology to the species level. Here, we present a brief summary of these undetermined cases with onset of symptoms from 2008 to 2012 reported to two passive surveillance systems in the United States. The reported incidence rate during this time was 0.52 cases per million person-years. Many cases (24%) had positive polymerase chain reaction results. Enhanced surveillance in an area where several of these etiologic agents are endemic may provide a better understanding of the epidemiology of ehrlichiosis and anaplasmosis in the United States.

Recently, we summarized data from passive surveillance on case reports of infections caused by *Ehrlichia chaffeensis*, *Ehrlichia ewingii*, and *Anaplasma phagocytophilum*.^{1,2} Although human ehrlichiosis and anaplasmosis are clinically similar, the enzootic cycle and epidemiology of these illnesses are distinct.³ In particular, *Amblyomma americanum* (the lone star tick) vectors *E. chaffeensis*, *E. ewingii*, and the Panola Mountain *Ehrlichia*, whereas *Ixodes scapularis* (the black-legged tick) is the primary vector for *A. phagocytophilum* and also a possible vector for *Ehrlichia muris*-like (EML) agent.^{4–8} The range of both the lone star tick and the black-legged tick have recently expanded, and both human ehrlichiosis and anaplasmosis may be endemic where both tick vectors are present.^{9,10} The discovery of human infections with the EML agent in the Upper Midwest, and with the Panola Mountain *Ehrlichia* species in Georgia, adds another layer to understanding the epidemiology of ehrlichiosis and anaplasmosis in the United States.^{7,8} Because definitive diagnostic laboratory evidence is not always available for cases of human ehrlichiosis and anaplasmosis, a catch-all reporting category—human ehrlichiosis/anaplasmosis undetermined—is used for passive surveillance, in addition to the specific reporting categories for infections with *E. chaffeensis*, *E. ewingii*, and *A. phagocytophilum*.¹¹ Here, we present a summary of these undetermined cases reported in the United States with onset of symptoms during 2008–2012.

Two passive surveillance systems collect data on these undetermined cases. The Nationally Notifiable Diseases Surveillance System (NNDSS) collects data on demographics and whether the case is classified as confirmed or probable. Additional information is reported on supplemental case report forms (CRFs): whether the case was clinically compatible, whether the case was hospitalized, whether the case survived, and diagnostic laboratory results. The distribution of case demographics reported is similar between the two systems, suggesting that one system is representative of the other

(Table 1). During 2008–2012, a total of 726 undetermined cases were reported through NNDSS from 44 states. Using U.S. Census Bureau population estimates to calculate the person-time at risk, the incidence rate was 0.52 cases per million person-years.^{12,13} County-level incidence rates are highest in the Upper Midwest where human anaplasmosis and EML incidence is highest; other states where multiple etiologic agents are endemic report undetermined cases (Figure 1). A total of 175 cases (24%) were reported with both unknown race and ethnicity through NNDSS and 106 cases (20%) were reported with both unknown race and ethnicity through CRFs. This incomplete reporting of race and ethnicity is similar to cases of human ehrlichiosis and anaplasmosis with determined etiology.^{1,2}

During 2008–2012, a total of 530 cases were reported through supplemental CRFs. A total of 11 cases (2%) reported infection with EML; and, an etiologic agent was not specified for the remaining 519 cases (98%). According to the Council of State and Territorial Epidemiologists (CSTE) case definitions, undetermined cases cannot be classified as confirmed.¹¹ However, 125 cases (24%) reported positive polymerase chain reaction (PCR) results, and 14 cases (2.6%) reported a 4-fold change in IgG titer by indirect immunofluorescence assay for *Ehrlichia* and/or *Anaplasma* antibodies. Some PCR assays are specific only to the genus level for *Ehrlichia* species.¹⁴ A positive result from these PCR assays does not meet the CSTE case definition for laboratory confirmed *E. ewingii* or *E. chaffeensis* infection, and therefore, these cases are reported as undetermined.¹¹ States may report PCR-positive cases as confirmed through NNDSS to differentiate them from cases reported with ambiguous serologic evidence (Table 1). The strong laboratory evidence reported with these cases underlines the difficulty in separating the epidemiology of ehrlichiosis and anaplasmosis by species.

There were no fatal cases reported through CRFs among the 440 cases (83%) with complete data during 2008–2012, whereas, the reported case fatality rate is 1% among infections with *E. chaffeensis* and 0.3% among cases of human anaplasmosis.^{1,2} Among the 442 cases (83%) with complete data, 184 cases (35%) reported being hospitalized, for a hospitalization rate of 42%. Similarly, 44 cases (8.3%) reported a life-threatening complication, including 16 cases of renal

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TABLE 1

Demographics of reported cases of human ehrlichiosis/anaplasmosis undetermined with onset of symptoms during 2008–2012 to the NNDSS and through supplemental CRFs

Characteristic	NNDSS (N = 726)	CRFs (N = 530)
	n (%)	n (%)
Sex		
Male	410 (56.5)	290 (54.7)
Female	310 (42.7)	237 (44.7)
Unknown	6 (0.8)	3 (0.6)
Race		
American Indian/Alaska native	2 (0.3)	1 (0.2)
Asian/Pacific Islander	4 (0.6)	2 (0.4)
Black	11 (1.5)	7 (1.3)
White	495 (68.2)	409 (77.2)
Other	17 (2.3)	—
Unknown	197 (27.1)	111 (20.9)
Ethnicity		
Hispanic	8 (1.1)	10 (1.9)
Not Hispanic	410 (56.5)	342 (64.5)
Unknown	308 (42.4)	178 (33.6)
Age (years)		
< 10	39 (5.4)	28 (5.3)
10–19	60 (8.3)	45 (8.5)
20–29	48 (6.6)	34 (6.4)
30–39	60 (8.3)	46 (8.7)
40–49	112 (15.4)	79 (14.9)
50–59	154 (21.2)	100 (18.9)
60–69	136 (18.7)	98 (18.5)
70+	116 (16.0)	83 (15.7)
Unknown	1 (0.1)	17 (3.2)
Case status		
Confirmed	133 (18.3)	—
Probable	592 (81.5)	530 (100)
Unknown	1 (0.1)	—

CRFs = case report forms; NNDSS = Nationally Notifiable Disease Surveillance System.

failure, 13 cases of meningitis or encephalitis, six cases of adult respiratory distress, three cases of pneumonia, and one case of disseminated intravascular coagulopathy. From our recent report, the hospitalization rate among human anaplasmosis cases was 31% and only 3% of cases reported a life-threatening condition.² Also, the hospitalization rate among *E. chaffeensis* infections was 57%, and 11% of cases reported a life-threatening

condition.¹ Therefore, these undetermined cases are not uniformly less severe than cases reported with an etiologic agent known at the species level.

Human undetermined ehrlichiosis/anaplasmosis remains a useful—albeit convoluted—notififiable condition in defining the epidemiology of ehrlichiosis and anaplasmosis in the United States. Future revisions to the case definitions for human ehrlichiosis and anaplasmosis will need to accommodate the growing list of etiologies and should aim to simplify the classification scheme in an effort to streamline and clarify reporting. Taking all the etiologies together, the reported incidence rate of human ehrlichiosis and anaplasmosis in the United States is 10 cases per million person-years, an increase of 40% from 2000 to 2007.^{1,2,15} Understanding the dynamic, complex epidemiology of these diseases has important consequences for guiding laboratory diagnostics development and usage and targeting public health messaging. Enhanced surveillance at sites where multiple agents of human ehrlichiosis and anaplasmosis are endemic may help interpret national trends in this catch-all category.

Received September 22, 2015. Accepted for publication October 19, 2015.

Published online November 30, 2015.

Acknowledgments: The ongoing work of clinicians, laboratorians, and public health professionals made this summary of national surveillance data possible, and we thank them for their devotion. We also thank Eric Mandel, John Krebs, and Jennifer McQuiston for their work in designing and building these data.

Financial support: This study was supported by the Centers for Disease Control and Prevention as well as 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 the Centers for Disease Control and Prevention.

Disclaimer: 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.

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FIGURE 1. Map of reported county incidence rates of human ehrlichiosis/anaplasmosis undetermined with onset of symptoms during 2008–2012. The number of cases is from the Nationally Notifiable Diseases Surveillance System, and person-time at risk is calculated using the U.S. Census Bureau population estimates.^{12,13} States are designated “NN” when undetermined cases were not notififiable for the duration of 2008–2012.

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