

Strongyloidiasis-Related Deaths in the United States, 1991–2006

Curtis Croker,* Roshan Reporter, Matt Redelings, and Laurene Mascola

Acute Communicable Disease Control Program, Los Angeles County
Department of Public Health, Los Angeles, California

Abstract. The objective of this study was to 1) assess the incidence of strongyloidiasis in the United States, 2) evaluate demographic and regional associations, and 3) identify comorbid conditions as risk factors for death. A population-based case-control study was performed by using mortality data during 1991–2006. We identified 347 strongyloidiasis deaths (0.79 per 10 million deaths, 14–29 deaths per year), which decreased slightly over time. Deaths occurred primarily among older (median age = 66.0 years), white (57.6%) and Hispanic (22.2%) men (69.2%), residing in the Southeastern United States (49.3%). Associated health conditions included chronic obstructive pulmonary disease (28.7%, odds ratio [OR] = 4.0, 95% confidence interval [CI] = 3.0–5.4) and infection with human immunodeficiency virus (12.5%, OR = 4.6, 95% CI = 2.7–7.9). Strongyloidiasis deaths in the second half of the study period (1999–2006) were less likely to be associated with chronic obstructive pulmonary disease (19.4%, OR = 1.2, 95% CI = 0.7–1.9), but continued to be associated with human immunodeficiency virus infection (12.9%, OR = 2.8, 95% CI = 1.3–6.0). Early detection and treatment of at-risk patients with latent strongyloidiasis infections is needed to reduce strongyloidiasis mortality.

INTRODUCTION

Strongyloides stercoralis is a nematode (roundworm) that infects persons on five continents and in at least 70 countries. Little is known about the true incidence of strongyloidiasis in the United States. Cases have been reported primarily from persons living in rural areas of the southeastern United States. Although dated, studies of strongyloidiasis in Kentucky and Tennessee indicated that prevalence rates can reach 3% in children and 6% in hospitalized patients when diagnosed by using stool examinations.^{1,2} Studies have also shown that cases in other regions of the United States, such as New York, Baltimore, Chicago and California, primarily occur among immigrants from developing countries or a United States territory such as Puerto Rico.^{3,4} The infection is most commonly acquired through skin contact with contaminated soil. The nematode is capable of replicating within the human host, enabling cycles of autoinfection that result in a prolonged gastrointestinal tract infection. Symptoms include larva currens, rash, and occasionally gastrointestinal symptoms, but many infections remain asymptomatic for decades, as exemplified by studies of latent infection in military veterans serving in the South Pacific and Far East.^{5,6}

As early as the 1950s, studies showed that under certain conditions, latent *Strongyloides* infection can become life threatening, and that these severe infections were becoming more common.⁷ This more severe infection can result in the increased presence of larvae in the pulmonary system (hyperinfection) and/or migration of larvae to organs beyond the range of the pulmonary autoinfection cycle (dissemination). Larvae penetrating the bowel mucosa facilitate the invasion of enteric bacteria into the circulation of the host, which can result in gram-negative sepsis and bacterial meningitis. Deaths in up to 87% of hyperinfected cases have been reported.⁴

Latent *Strongyloides* infection was well understood by the 1960s, and studies during this time suggested that corticosteroid treatments increase the severity of *Strongyloides* infection.⁸ Animal studies have reinforced this association.⁹ Additionally,

studies during this time also indicated that immunosuppressive illnesses such as hematologic malignancies may increase strongyloidiasis severity, which later studies have elaborated on.¹⁰ Since the 1960s, severe strongyloidiasis has been associated with a variety of immunosuppressive health conditions and/or health conditions that may require corticosteroid treatments, which include asthma,¹¹ arthritis,¹² lupus,¹³ inflammatory bowel disease (IBD),¹⁴ hypogammaglobulinemia,¹⁵ chronic obstructive pulmonary disease,¹⁶ sarcoidosis,¹⁷ acquired immunodeficiency syndrome/human immunodeficiency virus (HIV),^{18–25} and organ transplants.^{26,27} Many of these findings have been summarized by Genta.⁴

To assess the incidence of mortality caused by strongyloidiasis in the United States, and to evaluate demographics, regional differences, and comorbid conditions as risk factors for death, we performed a review of mortality data for all strongyloidiasis deaths in the United States from 1990 through 2006.

METHODS

A data set containing 16 years of strongyloidiasis deaths in the United States during 1991–2006 was created by using the multiple cause data set available from the National Center for Health Statistics.^{28–31} This data set was created by extracting information (age, sex, race/ethnicity, state of death, birth location, and cause(s) of death) from death certificates for each decedent. Strongyloidiasis-related deaths are defined as those listing International Classification of Diseases 9 (ICD-9) codes 127.2 (1990–1998) or ICD-10 codes B78-B78.9 (1999–2006) on the certificate as the underlying cause or a contributing cause of death. No distinction between the two species of *Strongyloides* (*S. stercoralis*, *S. fuelleborni*) is made in the mortality data. The distribution of deaths by the four regions in the United States (western, midwest, northeast, southeast) were compared.

The frequency of strongyloidiasis related mortality was analyzed by age, race/ethnicity, sex, and region. The overall age-adjusted rate was calculated using the year 2000 U.S. population as the standard population.³² To assess for possible comorbidity risk factors for strongyloidiasis-related deaths, we performed a nested case-control study. Diseases and conditions for the comorbidity analysis were selected on the basis of a review of published studies. Controls were randomly

*Address correspondence to Curtis Croker, Acute Communicable Disease Control Program, Los Angeles County Department of Public Health, 313 N. Figueroa, Los Angeles, CA 90012. E-mail: ccroker@ph.lacounty.gov

selected from non-strongyloidiasis deaths in the United States after matching for race/ethnicity, sex, region of residence, five-year age group, and within one year of death. We attempted to find five controls for each strongyloidiasis death. In five cases (1.4%), only four matches were identified. Variable ratio-matching techniques were used in calculating matched odds ratios so that these cases could still be used in the analysis. Two cases (0.3%) could not be matched and were excluded from the analysis. Mortality odds ratios (ORs) were calculated for assessed health conditions. All statistical analyses were performed by using SAS software version 9.1 (SAS Institute, Cary, NC).

RESULTS

We identified 347 strongyloidiasis-associated deaths occurring from 1991 through 2006, with 160 listing strongyloidiasis as an underlying cause of death (46%) and the remainder listing strongyloidiasis as a contributing cause. Strongyloidiasis deaths were primarily in older adults (mean age at death = 63.8 years, median = 66.0 years) who were white (57.6%) or Hispanic (22.2%) and more likely to be male (69.2%) than female (30.8%) (Table 1). Strongyloidiasis deaths were reported from 36 of the 50 states. However, nearly half (49.0%) resided in the southeastern United States, which included the states of Florida (9.9%), Louisiana (6.7%), and

Kentucky (6.1%). Non-Southern states reporting substantial numbers of deaths included California (13%), New York (7.3%), and Ohio (8.1%). The overall rate of strongyloidiasis-associated mortality for the study period was 0.79 per ten million deaths, decreasing slightly from the first half (0.92 per ten million deaths) to the last half (0.68 per ten million deaths) of the study period. Men had a higher mortality rate than woman (1.24 versus 0.45 per ten million deaths) and Asians had the highest mortality rate of the race-ethnicity groups reviewed here (3.83 per ten million deaths). Mortality rates were highest for persons 65–74 years of age (3.74 per ten million deaths).

Place of birth was available for 329 (94.8%) of the strongyloidiasis-related deaths. Most deaths occurred among persons born in the United States (62.3%), more specifically, born in a southeastern state (56.2%). Twenty-four percent of persons with strongyloidiasis were born in the states of Kentucky (n = 53) and Louisiana (n = 26). Place of death was available for all deaths. Deaths in the southeastern United States (n = 171) were primarily among white (77.2%), U.S. born (84.3%) persons, most of whom were born in the southeastern United States (83.7%). Deaths in the midwest (n = 61) were also most common among white (72.1%), U.S. born (74.1%) persons, but many (60.3%) were born in the southeastern United States. Deaths in the western United States (n = 59) were predominantly among persons of Asian ethnicity (52.5%) and among persons born outside the 50 states (70.9%). Deaths in the northeast (n = 56) were primarily among younger (mean age = 56.8 years versus 65.1 years), Hispanic (57.1%) men (80.4%) born outside the 50 states (88.0%). However, many (40.1%) of these persons were born in a U.S. territory.

Chronic pulmonary obstructive disease was the most prevalent health condition identified among strongyloidiasis deaths in this analysis (28.7%, n = 99) and was more likely to be associated with a strongyloidiasis death than a non-strongyloidiasis death (OR = 4.0, 95% confidence interval [CI] = 3.0–5.4) (Table 2). Strongyloidiasis deaths associated with COPD were more likely to occur among older (mean age = 70.2 years versus 63.2 years) persons born in the United States (45.7% versus 21.1%) than non-COPD-associated strongyloidiasis deaths. The COPD prevalence among strongyloidiasis deaths decreased from 36.3% in the first half of the study period (1991–1998) to 19.4% in the second half of the study period (1999–2006). The COPD prevalence among strongyloidiasis deaths was higher than that found among controls in the second half of the study period (19.4% versus 9.2%), but the association between COPD and strongyloidiasis was greatly decreased in the second half of the study period (OR = 1.2, 95% CI = 0.7–1.9).

The most prevalent immunosuppressive health condition identified among strongyloidiasis deaths was HIV (12.5%, n = 43), which was much less prevalent among non-strongyloidiasis deaths (3.5%) (OR = 4.6, 95% CI = 2.7–7.9). Strongyloidiasis deaths associated with HIV infection were more likely to be among younger (mean age = 43.2 years versus 65.2 years), Hispanic (62.8% versus 48.3%), foreign born (75.8% versus 32.9%) persons who were more likely to have died in the northeastern United States (32.6% versus 18.3%) than non-HIV associated strongyloidiasis deaths. The prevalence of strongyloidiasis deaths associated with HIV demonstrated a slight increase after the introduction of highly active antiretroviral therapy in 1995 (13.5% versus 9.3%), but there was little difference between the first half and last half of the study

TABLE 1

Demographics of strongyloidiasis mortality (347 deaths) in the United States, 1991–2006

Characteristic	No.	%	Age-adjusted mortality rate (per 10 million)	Mortality rate ratio
Overall	347	100.0	0.79	–
Early (1991–1998)	190	54.8	0.92	1.4
Late (1999–2006)	157	45.2	0.68	Referent
Race/ethnicity				
White	200	57.6	0.56	Referent
Hispanic	77	22.2	2.43	4.3
Asian	41	11.8	3.83	6.8
Black	29	8.4	0.61	1.1
Sex				
M	240	69.2	1.24	2.8
F	107	30.8	0.45	Referent
Age group, years				
15–34	14	4.0	0.11	Referent
35–44	31	8.9	0.45	4.0
45–54	36	10.4	0.63	5.6
55–64	72	20.7	1.84	16.4
65–74	111	32.0	3.74	33.4
75–84	71	20.5	3.71	33.1
≥ 85	12	3.5	0.18	1.6
Mean age, years (range)	63.8 (24–96)			
Median, years	66.0			
Place of death				
Southeast	171	49.3	1.09	1.8
West	59	17.0	0.60	1.0
Midwest	61	17.6	0.60	Referent
Northeast	56	16.1	0.66	1.1
Place of birth*				
U.S. 51 states	205	62.3		
Southeast	185	56.2	–	–
West	7	2.1	–	–
Midwest	8	2.4	–	–
Northeast	5	1.5	–	–
U.S. Territory	54	16.4		
Outside U.S.	70	21.3	–	–

*Place of birth was available for 94.8% of 329 deaths.

TABLE 2
Comorbidity data for strongyloidiasis mortality in the United States, 1991–2006*

Health condition	All cases (n = 345) and controls (n = 1,726) 1991–2006						Later cases (n = 155) and controls (n = 775) 1999–2006	
	Strongyloidiasis deaths (cases)		Non-strongyloidiasis deaths (controls†)		Matched odds ratio		Matched odds ratio	
	No.	%	No.	%	OR	95% CI	OR	95% CI
COPD	99	28.7	159	9.2	4.0	3.0–5.4	1.2	0.7–1.9
HIV	43	12.5	60	3.5	4.6	2.7–7.9	2.8	1.3–6.0
Hematologic malignancies	27	7.8	49	2.8	2.8	1.7–4.6	1.3	0.7–2.6
Lymphoma	14	4.1	39	2.3	3.1	1.8–5.3	1.9	1.0–3.5
Arthritis	16	4.6	35	2.0	2.2	1.2–4.0	1.2	0.5–2.8
Diabetes	17	4.9	161	9.3	0.5	0.3–0.8	0.3	0.2–0.7
Malignant neoplasms	59	17.1	536	31.1	0.4	0.3–0.6	0.3	0.2–0.4
Severe complications								
Septicemia	65	18.8	87	5.0	4.1	2.9–5.8	2.0	1.2–3.3
Shock (without trauma)	22	6.4	43	2.5	2.7	1.6–4.6	2.5	0.8–8.0

* OR = odds ratio; CI = confidence interval; COPD = chronic obstructive pulmonary disease; HIV = human immunodeficiency virus.

† Controls were selected from non-strongyloidiasis-related deaths and matched by sex, race/ethnicity, age (five-year age ranges), and U.S. geographic region of death. We attempted to find five matched controls for each case. Two cases were excluded from the matched odds ratio analysis because of incomplete values needed for matching, and 5 cases (1.4%) had less than five matched controls. These cases were still included in the matched odds ratio analysis.

period (12.1% versus 12.9%). Strongyloidiasis deaths associated with HIV included only 0.02% of the total HIV deaths for this period.

Hematologic malignancies were also identified more often among strongyloidiasis deaths (7.8%, n = 27) than non-strongyloidiasis deaths (2.8%, n = 49) (OR = 2.8, 95% CI = 1.7–4.6). A slight decrease in prevalence from the first half over the last half of the study period was noted (7.8% versus 6.3%), and the OR value for the second half of the study was closer to the null value (OR = 1.3, 95% CI = 0.7–2.6). Complications of septicemia and shock were also identified among strongyloidiasis deaths (18.8% and 6.4%, respectively) and were associated with strongyloidiasis deaths. Malignant neoplasms were less prevalent among persons who died of strongyloidiasis than among those who died of non-strongyloidiasis causes (17.1% versus 31.1%) as was diabetes (4.9% versus 9.3%). Other health conditions identified among strongyloidiasis deaths included arthritis (4.6%), asthma (3.5%), IBD (2.3%), bacterial meningitis (1.2%), sarcoidosis (0.9%), and lupus (0.6%). No organ transplants or cases of infection with human T cell lymphotropic virus type 1 were identified among strongyloidiasis deaths in this study.

DISCUSSION

The findings of this study indicate that strongyloidiasis deaths may be more common in the United States than previously appreciated. The number of strongyloidiasis deaths identified likely represent a minimal estimate of the true number, given the probability of under recognition of such deaths. Demographics of strongyloidiasis-associated deaths varied considerably by region in this study. Similarly, at-risk populations and exposures may also vary. As expected, most deaths occurred in the Southeastern United States among whites, whereas other regions revealed more deaths among Blacks, Asians, and Hispanics. The higher predominance of deaths among males is congruent with results of other studies,¹ as are racial and ethnic differences by U.S. region identified.

In the southeastern United States, most strongyloidiasis deaths occurred among older white men who were born in the southeast. These deaths most likely occurred among persons born among rural populations as other studies have shown.²

Infection may have been acquired from their rural place of residence or from service or travel abroad. The demographics of deaths in the midwest were similar to those in the southeast, but most persons who died of strongyloidiasis were born in the southeastern United States. Disseminated infection after treatment of conditions such as COPD and hematologic malignancy may develop in persons in these regions with latent strongyloidiasis infection. Deaths in the northeast were more likely to be in younger, foreign-born, Hispanic men, and associated with HIV infection or hematologic malignancy. Although exposure for this group likely occurred from their place of birth, sexual transmission among men who have sex with men may also be involved in the spread of disease in this population. Deaths in the west were more likely to be foreign-born persons of Asian descent who may have acquired their infection from their place of birth. Many of these deaths were associated with COPD and HIV infection.

Of the associated health conditions reviewed in this study, COPD was highly associated with strongyloidiasis deaths. This association seems intuitive, given the wide use of corticosteroids to treat COPD, and is consistent with findings in another study.¹⁶ The downward trend of this association in the second half of the study period may be a result of physicians screening at-risk patients before administering corticosteroid treatment and of improved steroid therapies that are targeted for specific functions of the body. Hematologic malignancies were also associated with strongyloidiasis deaths, as other studies have suggested.¹⁰ Surprisingly, strongyloidiasis deaths were less likely to be associated with diabetes and cancers in general compared with non-strongyloidiasis deaths. Illnesses such as diabetes and cancer may be less likely to be diagnosed in this population because of relatively low socioeconomic status¹ and lack of access to healthcare.

This study identified a strong association between HIV infection and strongyloidiasis deaths, especially in the northeast United States, where cases were more likely to be of Hispanic ethnicity. Winsberg and others conducted a *S. stercoralis* prevalence survey in a predominantly Puerto Rican neighborhood in Chicago, Illinois (n = 358) and identified 6 cases (1.7%) of strongyloidiasis by using single stool specimens.²² Given the limitation of using one stool specimen to detect strongyloidiasis, the true prevalence would be

expected to be higher. Another study reported a strongyloidiasis prevalence of 3.9% among 51 homosexual men visiting a sexually transmitted disease clinic in Baltimore, Maryland.²³ In comparison, a study of patients in Iran identified only 2 of 781 persons infected with HIV who were co-infected with strongyloidiasis;²⁴ both persons were in the progressive stage of HIV and showed signs of severe hyperinfection. Another study in London, United Kingdom, that examined the ratio of CD4 cells counts and strongyloidiasis incidence (n = 34) concluded that persons immunosuppressed by advancing HIV disease are not at increased risk for disseminated *Strongyloides* infection.¹⁸ A study of seven HIV cases in Brazil co-infected with *Strongyloides* infection reported that the relationship identified may be more related to steroid treatment of HIV patients than the disease.²⁵ Sexual transmission of *Strongyloides* has also been reported in other studies²³ and may be another explanation for the apparent association with HIV and predominance of men found in our study.

With the introduction of highly active antiretroviral therapy in 1995 for HIV patients, which extended the lives of infected persons, it might be expected that a decrease in opportunistic infections such as *Strongyloides* would occur. However, our data showed little change in HIV co-infection after 1995. The HIV association identified in our study may be caused by corticosteroid treatment, the immunosuppressive nature of the disease, the geographic origin of the patient where both diseases may be prevalent, or some combination of all of the above factors. Although immunocompromised conditions may exacerbate existing infection, they may also increase the likelihood of a new infection once a person is exposed and result in increased incidence in these groups.

Detecting and treating latent *Strongyloides* infection in at-risk persons is needed to prevent the transition to a life-threatening disease. However, latent *Strongyloides* infection can be difficult to diagnose, with less than half of cases detectable by a single stool microscopy examination, and the only consistent diagnostic feature of infection is eosinophilia.^{33–37} Enzyme-linked immunosorbent assay laboratory techniques are reported to have a specificity and sensitivity of 93% and 95%, respectively, for at-risk populations or persons in disease-endemic communities.³⁶ This laboratory technique has been found to be a useful tool for diagnosing and monitoring response to adequate treatment in at-risk populations. However, a high number of false-positives results will occur when the test is used as a screening tool in a community in a non-endemic region. Additional studies are needed to determine the utility of the *Strongyloides* enzyme-linked immunosorbent assay as a monitoring tool to evaluate effectiveness of treatment. Other diagnostic tools include tissue biopsies obtained through the use of an endoscope or bronchoscope, which are capable of recovering *Strongyloides* larva.³⁷ Treatment usually consists of an anthelmintic drug such as ivermectin, with longer dosing required for hyperinfected patients. However, optimal treatment time is a topic of much discussion.³⁸

An unanticipated finding in our study was the lack of association between transplant recipients and strongyloidiasis mortality. Other case studies have identified *Strongyloides* hyperinfection in persons undergoing immunosuppression post-organ transplant caused by either an underlying latent infection or an infected transplanted organ.^{26,27} One explanation for the lack of association found in our analysis is the

combination of under-reporting of health conditions on death certificates in general,²⁸ and that mortality caused by strongyloidiasis and mortality caused by organ transplants in the United States are relatively rare events. Another explanation is that with the introduction of cyclosporine in the 1990s as a post-transplant immunosuppressant drug, there are fewer transplant cases associated with *Strongyloides* hyperinfection, as reported.^{26,27} Some studies indicate that cyclosporine has an antihelminthic effect against *S. stercoralis*.²⁷ In addition, the ICD9-10 codes used in this study for organ transplants may not have been sufficient to capture this association or were not used by clinicians recording such deaths.

Strongyloidiasis is a large problem globally and is under-recognized in the United States. This study demonstrates that the demographics of deaths caused by strongyloidiasis may vary greatly by region in the United States and should be considered when clinicians screen patients for this latent infection before administering immunosuppressive therapy. Deaths in the United States primarily affect older male adults living in the southeastern region, and strongyloidiasis mortality remained relatively unchanged over the 15-year study period. This study found that co-infection with HIV among persons who died of strongyloidiasis is more prevalent than other studies would have indicated, especially among deaths in the northeastern United States. Future research is needed to clarify this identified association. Clinicians should screen for HIV and for other health conditions reviewed in this study before administering corticosteroid treatment to at-risk patients to prevent disseminated infection. At-risk patients include persons born in, serving in, or traveling to areas where the parasite is endemic, which include rural areas of sub-Saharan Africa, Southeast Asia, Latin America, and some parts of the southeastern United States.

The results of our study are limited by lack of information regarding the chronological order of conditions on the death certificate. Our assumption in this study is that strongyloidiasis develops first, exacerbated by an immunosuppressive or health condition requiring immunosuppressive therapy. However, the data do not explicitly indicate this suggestion. Also, assessing for disease association in living persons by analyzing disease associations among persons who have died is more convenient. However, this analysis may produce results that are more limited because the information analyzed may be of lesser quality. Misclassification of demographic information on death certificates and in census data may also lead to distorted mortality rate estimates that do not accurately reflect true differences in disease incidence in the population. Moreover, errors may occur in completing the cause of death section of the death record, which can lead to variations in the death certificate information. Potentially, persons may be exposed to both diseases in disease-endemic regions and severe illness resulting from one infection may lead to the diagnosis of the other disease, although there may be no causal association between the two diseases.

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Authors' address: Curtis Croker, Roshan Reporter, Matt Redelings, and Laurene Mascola, Acute Communicable Disease Control Program, Los Angeles County Department of Public Health, Los Angeles, CA.

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