

# Coccidioidomycosis-associated Deaths, United States, 1990–2008

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### Learning Objectives

Upon completion of this activity, participants will be able to:

- Assess the epidemiology of coccidioidomycosis
- Evaluate the transmission and clinical course of coccidioidomycosis
- Analyze demographic risk factors for mortality in cases of coccidioidomycosis
- Distinguish comorbid conditions associated with a higher risk of mortality in cases of coccidioidomycosis

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Coccidioidomycosis is endemic to the Americas; however, data on deaths caused by this disease are limited. To determine the rate of coccidioidomycosis-associated deaths in the United States, we examined multiple cause-coded death records for 1990–2008 for demographics, secular trends, and geographic distribution. Deaths were identified by International Classification of Diseases, 9th and 10th Revision, codes, and mortality rates were calculated. Associations of deaths among persons with selected concurrent conditions were examined and compared with deaths among a control group who did not have coccidioidomycosis. During the 18-year period, 3,089

coccidioidomycosis-associated deaths occurred among US residents. The overall age-adjusted mortality rate was 0.59 per 1 million person-years; 55,264 potential life-years were lost. Those at highest risk for death were men, persons >65 years, Hispanics, Native Americans, and residents of California or Arizona. Common concurrent conditions were HIV and other immunosuppressive conditions. The number of deaths from coccidioidomycosis might be greater than currently appreciated.

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Coccidioidomycosis is a reemerging infectious disease caused by inhalation of airborne spores of the soil fungus *Coccidioides immitis* or *C. posadasii* (*I. Coccidioides* spp. are native to arid and desert areas in North America (California, Arizona, Texas, Utah, Nevada,

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New Mexico, and northern parts of Mexico), Central America, and South America (2). The manifestations of infection with either organism are assumed to be identical. *Coccidioides* spp. are found in lower elevation areas that receive <20 inches of rain per year and have warm, sandy soil (3). They are usually found 4–12 inches below the surface. Organism growth is enhanced in areas of animal droppings, burial sites, and animal burrows (4). Among persons living in coccidioidomycosis-endemic areas, ≈10%–50% have been exposed to *Coccidioides* spp. Each year in the United States, an estimated 150,000 new cases of coccidioidomycosis occur (5). The trend of incidence varies by state because of differences in epidemiology, reporting standards, and case definitions. For 2010, the 2 states most affected by coccidioidomycosis, Arizona and California, reported incidence of 186.0 and 11.5 cases per 100,000 population, respectively (6–8).

The epidemiology of coccidioidomycosis varies by area; environmental factors play a major role (9). Exposure to *Coccidioides* spp. varies by season, geographic location (3), and condition of the air. Exposure to spores is more common in dusty conditions, e.g., after earthquakes, dust storms, droughts, and other natural disasters that increase the amount of dust in the air (10). Persons in certain occupations are at higher risk for exposure to spores, e.g., archeologists (11), military personnel, construction workers (12), and farmers. Prisons in coccidioidomycosis-endemic areas might place inmates at risk for exposure (13).

Pulmonary infection can result from inhalation of 1 spore; however, high numbers of spores are more likely to result in symptomatic disease. With rare exception, animal-to-person or person-to-person transmission does not occur. The incubation period is 1–4 weeks. Most patients are asymptomatic, but others might have an acute or chronic disease that initially resembles a protracted respiratory or pneumonia-like febrile illness primarily involving the bronchopulmonary system. Dissemination to multiple organ systems can occur. Illness is typically characterized by ≥1 of the following: influenza-like signs and symptoms; pulmonary lesion diagnosed by chest radiograph; erythema nodosum or erythema multiforme rash; meningitis; or involvement of bones, joints, skin, viscera, and lymph nodes (14,15). Extrapulmonary manifestations occur in 0.6% of the general population, most commonly secondary to hematogenous spread; meningitis carries an especially grave prognosis (16). The risk for disseminated disease is significantly higher among men (17), those with compromised or suppressed immune systems (e.g., persons with HIV), those receiving corticosteroids, and pregnant women. Risk for disseminated disease also seems to be higher for African Americans and Filipino Americans (18).

Despite the potential for coccidioidomycosis to be severe and fatal, studies of deaths associated with

coccidioidomycosis in the United States are limited (19,20). To determine possible risk factors for coccidioidomycosis-associated death, we used US multiple-cause-of-death data to assess demographics, secular trends, geographic distribution, and concurrent conditions.

## Methods

### Data Sources

We analyzed de-identified, publicly available multiple-cause-of-death data from US death certificates from the National Center for Health Statistics for 1990–2008 (21,22). These death records contained demographic information for each decedent (including age, sex, and race/ethnicity) and geographic information (state of residence and place of death). In addition to designating underlying causes, the physician or coroner can list conditions that are believed to have contributed to the death. These conditions were coded according to the International Classification of Diseases, 9th Revision (ICD-9), for 1990–1998 and International Classification of Diseases, 10th Revision (ICD-10), for 1999–2008 (23,24). A coccidioidomycosis-associated death was defined as death of a US resident with an ICD-9 code of 114.0–114.9 or an ICD-10 code B38.0–B38.9 listed as an underlying or contributing cause on the death record (21,25).

### Mortality Rates and Trends

We calculated mortality rates and 95% CIs by using bridged-race population estimates derived from US census data, and we subsequently age-adjusted these rates with weights from the 2000 US standard population data. Mortality rates and rate ratios were calculated by a decedent's race/ethnicity (white, black, Hispanic, Asian, Native American), year of death, and state of residence by using aggregated data from all years of study to ensure stable rates. Years of potential life lost were calculated by subtracting age at death from 75 for all who died before 75 years of age (26). This method was used for consistency with the Centers for Disease Control and Prevention Web-based Injury and Statistics Query and Reporting System (27).

### Analysis of Concurrent Illnesses

To identify possible risk factors for coccidioidomycosis-associated death, concurrent conditions that were noted on the death records were compared with those noted on the records of a control group whose deaths were not associated with coccidioidomycosis. Five control decedents were randomly selected and matched to each coccidioidomycosis decedent by 5-year age group, sex, and race. Matched odds ratios and 95% CIs were computed. Concurrent conditions were chosen

on the basis of biological plausibility and known or suspected risk factors for death from coccidioidomycosis. Concurrent conditions were identified on the death record as either an underlying or contributing cause (21,25). All analyses were conducted by using SAS 9.2 software (SAS Institute, Inc, Cary, NC, USA).

## Results

### Demographics

During 1990–2008, a total of 3,089 coccidioidomycosis-associated deaths among US residents were identified; these deaths represent 55,264 years of potential life lost. The overall crude mortality rate was 0.58 per 1 million person-years (95% CI 0.56–0.61); after age adjustment, the mortality rate was 0.59 deaths per 1 million person-years (95% CI 0.57–0.61). Age-adjusted mortality rates, by year, are shown in Figure 1. A total of 2,202 (>70%) decedents were men, and 887 (28.7%) were women; age-adjusted mortality rates were 0.94 per 1 million person-years and 0.32 per 1 million person-years, respectively. Death associated with coccidioidomycosis was 2.04× (95% CI 2.84–3.26) more likely for men than for women.

Mortality rates were higher for decedents >65 years of age than for those in other age groups (Table 1). Most (603 [19.5%]) deaths occurred at 65–74 years of age; age-specific mortality rate was 1.70 per 1 million person-years. Although the 206 decedents >85 years of age represented only 6.7% of the total deaths, the mortality rate was highest for this group (2.56 deaths/1 million person-years).

Most decedents whose death was associated with coccidioidomycosis were white (1,693 [54.8%]), 747 (24.2%) were Hispanic, 392 (12.7%) were black, 178 (5.8%) were Asian, and 79 (2.6%) were Native American (Table 2). Age-adjusted mortality rate was highest among Native Americans (2.56 deaths/1 million person-years), followed by Hispanics (1.77 deaths/1 million person-years) and lowest among whites (0.40 deaths/1 million person-years). Age-adjusted race-specific rates were elevated for all nonwhite groups. The likelihood of dying with coccidioidomycosis listed on the death record was 6.34× (95% CI 6.04–6.65) greater for Native Americans, 4.38× (95% CI 4.17–4.60) greater for Hispanics, 2.82× (95% CI 2.69–2.97) greater for Asians, and 1.70× (95% CI 1.61–1.80) greater for blacks than for whites.

### Geographic Associations

All states reported coccidioidomycosis-associated deaths; however, most deaths occurred in California (1,451 [47.0%]) and Arizona (1,010 [32.7%]); age-adjusted mortality rates were 2.47 (95% CI 2.35–2.60) and 10.60 (95% CI 9.94–11.25) deaths per 1 million person-years,

respectively (Figure 2). No notable temporal or seasonal trends were observed.

### Disease Associations

Several conditions were more commonly represented on the death records of those whose death was associated with coccidioidomycosis than on the death records of matched controls whose death was not associated (Table 2.) These conditions are vasculitis (matched odds ratio [MOR] 6.55, 95% CI 3.85–11.12), rheumatoid arthritis (MOR 6.51, 95% CI 4.05–10.45), systemic lupus erythematosus (MOR 4.17, 95% CI 2.52–6.90), HIV infection (MOR 3.92, 95% CI 3.24–4.75), tuberculosis (MOR 2.82, 95% CI 1.66–4.79), diabetes mellitus (MOR 2.12, 95% CI 1.86–2.42), chronic obstructive pulmonary disease (MOR 1.45, 95% CI 1.25–1.68), and non-Hodgkin lymphoma (MOR 1.44, 95% CI 1.03–2.01).

### Discussion

The number of coccidioidomycosis-associated deaths in the United States is appreciable. Mortality rates were highest in persons >65 years of age, men, Native Americans, and Hispanics. Since 1997, however, coccidioidomycosis-related mortality rates have been relatively stable.

The increased risk for coccidioidomycosis-associated death among older persons might reflect decreasing immune function and increased prevalence of concurrent diseases. Increasing age has been identified as a potential risk factor for infection with *Coccidioides* spp. (28). The increased rate of coccidioidomycosis-associated deaths observed among men might reflect their higher risk for severe pulmonary and disseminated coccidioidomycosis (17). The occupations associated with coccidioidomycosis (agricultural work, construction work, military service, and work at archeological sites) might also play an additional role (10–12) in the high numbers of coccidioidomycosis-associated deaths among men.

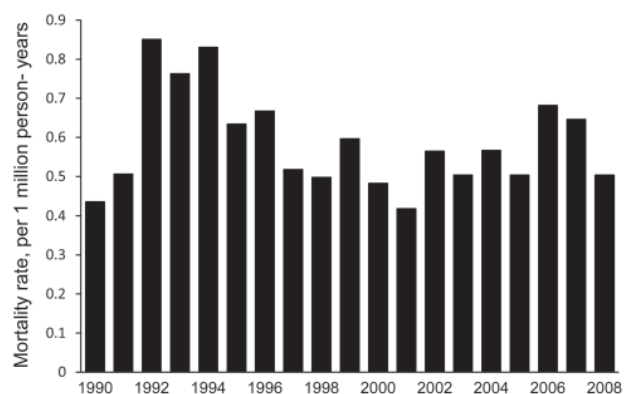


Figure 1. Age-adjusted mortality rates of coccidioidomycosis, per 1 million persons in the United States, by year, 1990–2008.

## RESEARCH

Table 1. Demographic characteristics, mortality rates, and rate ratios for coccidioidomycosis-associated deaths, United States, 1990–2008\*

Characteristic	No. (%)	Age-adjusted mortality rate (95% CI)†	Age-adjusted rate ratio (95% CI)
Overall	3,089 (100)	0.59 (0.57–0.61)	NA
Sex			
F	887 (28.7)	0.31 (0.29–0.33)	Referent
M	2,202 (71.3)	0.93 (0.90–0.98)	3.04 (2.84–3.26)
Race/ethnicity			
White	1,693 (54.8)	0.40 (0.38–0.42)	Referent
Hispanic	747 (24.2)	1.77 (1.63–1.90)	4.38 (4.17–4.60)
Black	392 (12.7)	0.69 (0.62–0.75)	1.70 (1.61–1.80)
Asian	178 (5.8)	1.14 (0.96–1.32)	2.82 (2.69–2.97)
Native American	79 (2.6)	2.56 (1.96–3.15)	6.34 (6.04–6.65)
Age, y			
0–4	8 (0.3)	0.11 (0.03–0.18)	NA
5–14	12 (0.4)	0.02 (0.01–0.03)	NA
15–24	94 (3.0)	0.13 (0.10–0.15)	NA
25–34	302 (9.8)	0.39 (0.34–0.43)	NA
35–44	368 (11.9)	0.45 (0.40–0.50)	NA
45–54	453 (14.7)	0.66 (0.60–0.73)	NA
55–64	490 (15.9)	1.02 (0.93–1.11)	NA
65–74	603 (19.5)	1.70 (1.56–1.84)	NA
75–84	553 (17.9)	2.43 (2.23–2.64)	NA
>85	206 (6.7)	2.56 (2.21–2.91)	NA

\*NA, not applicable.

†Crude rates are used for the age category.

Age-adjusted, race-specific, coccidioidomycosis-associated mortality rates were highest for Native Americans and Hispanics; these rates probably reflect the higher density of American Indian and Hispanic populations living in areas that are arid and where coccidioidomycosis is endemic. All the coccidioidomycosis-associated deaths of Native Americans occurred in the western region of the United States. Some literature sources have suggested that Native Americans are at increased risk for exposure to *Coccidioides* spp. because of cultural practices and exposure to contaminated dust (11). Poor access to health care services might delay diagnosis, resulting in more severe disease. The high rates observed among Native Americans must be interpreted with caution, given the relatively small number of deaths.

Coccidioidomycosis-associated mortality rates were also higher among blacks and Asians than among whites but lower than rates among Native Americans and Hispanics. Black race and Filipino ancestry are recognized risk factors for disseminated disease (2). We were unable to ascertain coccidioidomycosis-associated mortality rates for Filipino Americans. These higher mortality rates

might reflect an increased risk for severe disease, greater risk for exposure, or both.

That coccidioidomycosis-associated mortality rates are highest in Arizona and California is expected, given that *Coccidioides* spp. are endemic to these regions. These 2 regions are also classic retirement magnets; they attract elderly persons to migrate and settle down (29), thereby introducing new, unexposed populations to *Coccidioides* spp. Every state recorded coccidioidomycosis-associated deaths, which probably reflects population mobility and movement in and out of coccidioidomycosis-endemic areas after exposure.

Chronic illnesses have changed the way opportunistic mycoses affect the population. The conditions that were associated with coccidioidomycosis were all inherently associated with immunosuppression: HIV, tuberculosis, diabetes mellitus, autoimmune diseases, organ transplant, and cancers of lymphatic cells (30–38). Despite relatively low numbers of cases, an association was found between coccidioidomycosis-associated deaths and lupus erythematosus, vasculitis, and rheumatoid arthritis.

Table 2. Concurrent conditions listed with coccidioidomycosis on death records, United States, 1990–2008\*

Disease	ICD 9 code	ICD 10 code	No. deaths	Matched odds ratio
Vasculitis	446, 447.6	I776, I80, L95, M39, M31	36	6.55 (3.85–11.12)
Rheumatoid arthritis	714	M05-M06	45	6.51 (4.05–10.45)
Systemic lupus erythematosus	710	M32.0-M32.9	31	4.17 (2.52–6.90)
HIV infection	042–0449	B20-B24	253	3.92 (3.24–4.75)
Tuberculosis	010.0–018.9	A16-A19	24	2.82 (1.66–4.79)
Diabetes mellitus	250.0–250.9	E11-E14	384	2.12 (1.86–2.42)
Chronic obstructive pulmonary disease	490–492, 494–496	J40-J44, J47	287	1.45 (1.25–1.68)
Non-Hodgkin lymphoma	202, 200	C82-C85	47	1.44 (1.03–2.01)

\*ICD, International Classification of Diseases.

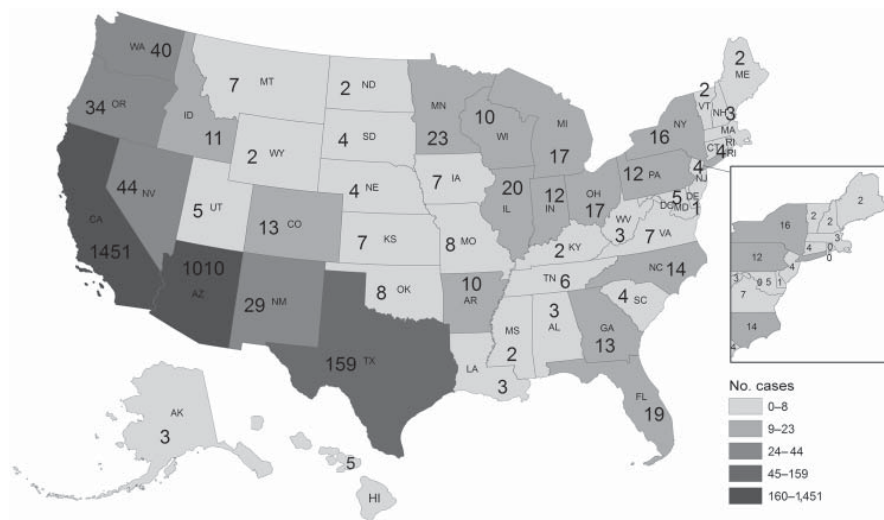


Figure 2. Number of coccidioidomycosis-associated deaths and age-adjusted rates per 1 million persons in the United States, 1990–2008.

Several limitations are inherent when multiple-cause-of-death data are used. Although these data are population based and contain large numbers of observations, death certificates probably underreport causes of death and can contain errors, which have been attributed to a variety of factors (39). Mortality rates can be distorted because of errors in population estimates, particularly for race/ethnicity. Because estimates of the at-risk population factor into the denominator for rate calculations, such errors can lead to biased estimates. Although inferential statistics are not designed for use with population-based data, 95% CIs demonstrate that error does exist in the mortality rates and rate ratios reported here. We urge caution in the strict interpretation of our values.

Coccidioidomycosis remains a major cause of death in the United States. Given the growing US population of elderly and immunosuppressed persons, the number of coccidioidomycosis-related deaths will probably increase, resulting in higher costs to the health care system (38). Effects of increasing health care costs associated with coccidioidomycosis have been observed in coccidioidomycosis-endemic states; almost half of the reported case-patients are hospitalized and make multiple visits to emergency rooms and outpatient facilities during the course of the illness (15). Physicians should be aware of the increased risk for coccidioidomycosis-associated death among those who are immunosuppressed, elderly, male, Hispanic, and/or Native American. For identifying suspected cases, an accurate travel exposure and occupational history are crucial, especially in persons from non-coccidioidomycosis-endemic areas. Further investigation into measures that will effectively decrease coccidioidomycosis exposure risk to the general public is needed, as are more studies of health disparities that surround coccidioidomycosis-associated deaths.

During the study, Ms Huang was a Master's of Public Health student at the University of Southern California. Her research interests include fungal disease epidemiology and association of comorbid chronic conditions with infectious diseases.

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