Public Health Surveillance for Coccidioidomycosis in Arizona

REBECCA H. SUNENSHINE,[a,b] SHOANA ANDERSON,[a] LAURA ERHART,[a] ANNE VOSSBRINK,[a] PETER C. KELLY,[a] DAVID ENGELTHALER,[a] AND KENNETH KOMATSU[a]

[a]*Arizona Department of Health Services, Phoenix, Arizona, USA*

[b]*Centers for Disease Control and Prevention, Atlanta, Georgia, USA*

ABSTRACT: Coccidioidomycosis or Valley Fever is a fungal disease that occurs primarily in the southwestern United States. Of the estimated 150,000 U. S. coccidioidomycosis infections per year, approximately 60% occur in Arizona, making this state the focal point for investigation of the disease. In this manuscript, we describe the epidemiology of coccidioidomycosis reported in Arizona over the last decade, hypotheses for the findings, and Arizona's response to the rising epidemic. Coccidioidomycosis surveillance data in Arizona consist of basic demographics of all laboratory and physician-diagnosed cases, the reporting of which has been mandated by law since 1997. The rate of reported coccidioidomycosis has more than quadrupled over the last decade from 21 cases per 100,000 population in 1997 to 91 cases per 100,000 in 2006 ($P < 0.001$). Case rates in older age groups ($\geq$65 years old) have more than doubled since 2000 ($P < 0.001$). These data demonstrate the rising coccidioidomycosis epidemic in Arizona, especially among the elderly. The increase in the numbers of reported cases can be partially explained by the institution of mandatory laboratory reporting in 1997, but the cause of the persistent rise after 1999 is unknown. Further investigation of coccidioidomycosis will not only assist with the development of public health interventions to control this disease in Arizona and the southwestern United States, but will also provide important information to prepare for a bioterrorism event caused by this select agent.

KEYWORDS: coccidioidomycosis; lung diseases; fungal; epidemiology

INTRODUCTION

Of the estimated 150,000 infections with *Coccidioides* spp. per year in the United States,[1] approximately 60% occur in people who live in Arizona.[2]

Address for correspondence: Rebecca Sunenshine, M.D., Arizona Department of Health Services, 150 N. 18th Ave, Suite 150, Phoenix, AZ 85007. Voice: 602-768-1682; fax: 602-542-2722. Sunensr@azdhs.gov

Ann. N.Y. Acad. Sci. 1111: 96–102 (2007).
doi: 10.1196/annals.1406.045

Prior to 1997, the Arizona Department of Health Services (ADHS) required only physicians to report coccidioidomycosis cases. Because of the increasing numbers of reported coccidioidomycosis cases,[3] ADHS instituted mandatory reporting of coccidioidomycosis by both laboratories and physicians in 1997. This led to a sharp increase in reported cases of coccidioidomycosis in addition to improving the timeliness and completeness of coccidioidomycosis reporting. In this manuscript, we describe the epidemiology of reported coccidioidomycosis in Arizona over the last decade, hypotheses for the findings, and Arizona's response to the rising epidemic.

METHODS

Clinical laboratories in Arizona routinely submit coccidioidomycosis blood serology results to ADHS using the U.S. postal service, fax, or by courier, depending on the laboratory. Additionally, providers are required to report patients they diagnose, treat, or detect with coccidioidomycosis to the local health agency, who subsequently report to ADHS.

All surveillance data from both laboratories and providers were collected on standard forms, entered into Arizona's Medical Electronic Disease Surveillance and Intelligence System on Microsoft Access or Excel, and analyzed using SAS (SAS Institute, Cary, NC, USA) software. Rates are calculated using Arizona census population data from the respective year as the denominator, except for 2006, which uses the 2005 census data as the denominator. The Mantel–Haenszel chi-square test was used to determine odds ratios for categorical variables. All statistical tests were two-tailed; a *P*-value of 0.05 or less was considered significant.

The case definition used by ADHS for a confirmed coccidioidomycosis case includes at least one of the following laboratory confirmatory tests:

- Cultural, histopathologic, or molecular evidence of the presence of *C. immitis*, or *C. posadasii*
- Immunologic evidence of infection (All titers must be $\geq$ 1:4)
  1. Serologic (testing of serum, cerebrospinal fluid, or other body fluid):
     (a). detection of coccidioidal IgM by immunodiffusion, enzyme immunoassay (EIA), latex agglutination, or tube precipitin, or
     (b). detection of any titer of coccidioidal IgG by immunodiffusion, enzyme immunoassay (EIA), or complement fixation
  2. Coccidioidal skin test conversion from negative to positive after the onset of clinical signs and symptoms (reagent not currently available)

Data submitted from the laboratories include the patient's name and birth date; date of report; laboratory result, specimen type and site, if applicable; and

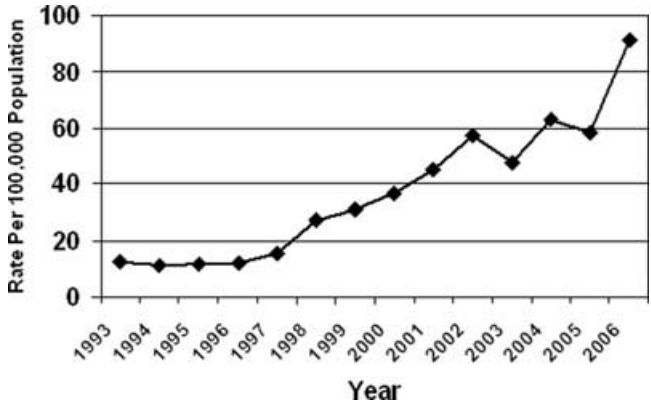

FIGURE 1. Rates of reported coccidioidomycosis by year in Arizona, 1993–2006.

sometimes race/ethnicity. Epidemiologists at ADHS input, review, and analyze these data weekly.

Mortality due to coccidioidomycosis is obtained from death certificate data, which originates directly from the ADHS Office of Vital Records. If a death is due to coccidioidomycosis and is not recorded as either the primary or a contributing cause of death on the death certificate, the information would not be captured by our surveillance system.

RESULTS

The rate of reported coccidioidomycosis cases in Arizona increased from a base line of approximately 21 cases per 100,000 population in 1997 (958 total cases) to 37 cases per 100,000 population (1,812 total cases) in 1999 ($P < 0.001$) after the institution of mandatory laboratory reporting in 1997 (FIG. 1). Thereafter, the rate of reported coccidioidomycosis trended upward annually to a peak of 91 cases per 100,000 in 2006 ($P < 0.001$) for a total 5,535 cases in 2006.

The sex distribution of reported coccidioidomycosis cases in Arizona has consistently demonstrated a slight male preponderance and has not changed over time as is described in the literature[4] (55% males in 2005); however, the number of cases by age group has changed considerably over time (FIG. 2). The case rates in older age groups ($\geq$65 years old) progressively increased from 83 in 2000 to 206 per 100,000 population in 2006 ($P < 0.001$). This means that the coccidioidomycosis incidence in the elderly has more than doubled over a 7-year period.

The average rate of reported coccidioidomycosis cases in Arizona in 2005 was 58 per 100,000, with the majority consistently occurring in Maricopa, Pima, and Pinal counties, Arizona's most densely populated urban counties

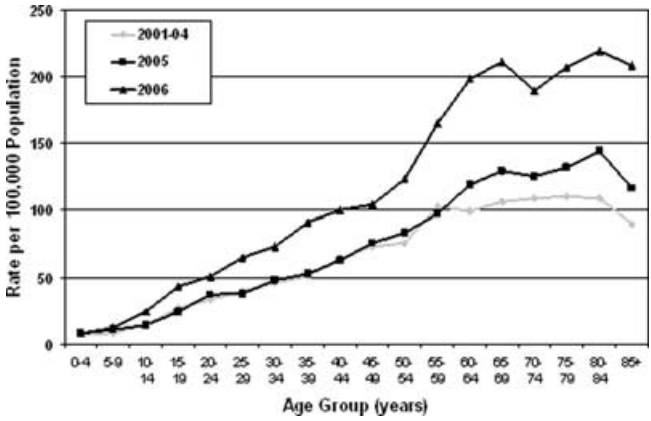

FIGURE 2. Coccidioidomycosis rates per 100,000 by age and year, Arizona, 2001–2006.

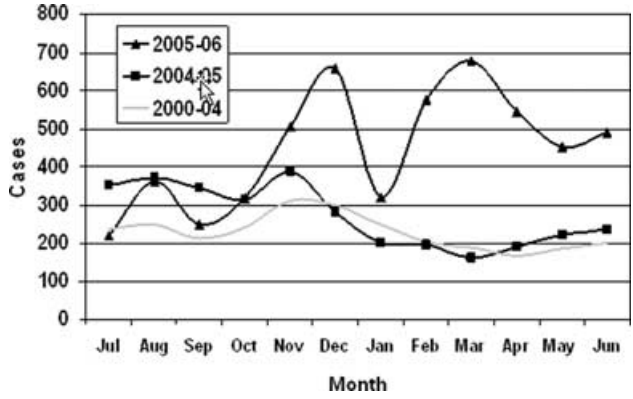

FIGURE 3. Reported coccidioidomycosis cases by month, Arizona, 2000–2006.

in the Mediterranean climatic zone (67.5, 78.3, and 63.7 cases per 100,000, respectively). Maricopa and Pima Counties contain the two largest cities in Arizona, Phoenix and Tucson, respectively.

Coccidioidomycosis has demonstrated a seasonal pattern in Arizona, which typically presents as a pronounced early winter peak from October to January and a smaller summer peak from May to August. The surveillance data from 2000 to 2004 reflect this pattern (FIG. 3). In the year from July 2004 to June 2005, we observed a more pronounced, yet shorter winter peak and a very small summer peak. In contrast, 2005–2006 data exhibit remarkably high summer and winter peaks, well beyond those in the previous 5 years.

The total number of deaths due to coccidioidomycosis has remained essentially unchanged over the last decade, with approximately 30 reported each year (mean and median 28.5, range 23–41). The mortality associated with

coccidioidomycosis has actually decreased because of the rising population in Arizona (from 0.9 in 1996 to 0.5 in 2005 per 100,000 population).

DISCUSSION

The ADHS surveillance data demonstrate a steady increase in reported coccidioidomycosis cases, with pronounced demographic and seasonal changes over the last decade. These data prompt a number of questions, the majority of which can only be answered with further investigation.

First, does the increase in reported cases represent an actual increase in coccidioidomycosis in Arizona or is it an artifact of increased reporting or testing? Of note, the population of Arizona has risen steadily from 4.6 million in 1997 to 6.0 million in 2005, whereas the reported rates of coccidioidomycosis have increased even when taking the population into account. The initiation of mandatory laboratory reporting could certainly explain the initial increase in cases after 1997; however, it is unlikely to explain increases after 1999. Our rules for laboratory reporting have not changed since 1997 and although completeness of physician reporting has been historically questionable, no evidence suggests improvement in physician reporting over the last decade.

Regarding the possibility of increased testing by physicians, an investigation performed by Chang and colleagues in two large Phoenix outpatient clinics indicate that $<15\%$ of patients with community-acquired pneumonia (CAP), a common presentation of coccidioidomycosis,[5] are tested for the disease.[6] Unfortunately, no statewide data are available regarding current coccidioidomycosis testing practices.

Assuming the increase in coccidioidomycosis reporting represents an actual increase in disease incidence, what is the cause? Numerous factors have been hypothesized, including soil disturbance due to construction of new homes for the rapidly rising population in Arizona;[2,7] climate variations, including changes in temperature and precipitation, in different seasons, which have been shown to be important predictors of coccidioidomycosis incidence;[7–10] and windstorms leading to increased dust exposure.[11] Unfortunately, further research needs to be done to determine why coccidioidomycosis has reached epidemic proportions in Arizona.

Why has the incidence of disease specifically increased in the elderly? Although the population of Arizona has increased in age over the last decade, rates among persons aged $\geq$ 65 years have continued to increase, despite age adjustment. One hypothesis is that older individuals are more likely to have health insurance and therefore seek medical care, which may increase their likelihood of being diagnosed with coccidioidomycosis. A second is that persons aged 65 years and older are more susceptible to developing symptomatic disease. A third is that the increased migration of individuals at retirement age to Arizona from nonendemic areas may be leading to a more susceptible

elderly population. Again, further study is required to elucidate whether any of these hypotheses has merit.

An additional question raised is why the mortality due to coccidioidomycosis has actually decreased when reported rates of the disease have increased. One possible explanation is that mortality data obtained from death certificates often underestimate actual disease mortality since physicians often fill out death certificates incorrectly.[12,13] Another possibility, however, is that treatment for coccidioidomycosis and medical care in general has improved substantially, allowing patients to survive longer. Alternatively, there could be a disproportionate increase in the diagnosis of primary pulmonary coccidioidomycosis, filling in a portion of the "iceberg" of total cases previously undiagnosed, as physician and patient awareness increase with the recent media coverage of Arizona's coccidioidomycosis epidemic.

Finally, what is ADHS doing about this important public health issue? First, an ongoing physician-education program has been established to raise awareness among health-care providers about the increase in coccidioidomycosis and its tendency to present as CAP.[5] Secondly, in May 2006, ADHS issued the recommendation to test all patients with CAP in endemic areas of Arizona for coccidioidomycosis. ADHS is also working with partners at the Centers for Disease Control and Prevention to better determine the percentage of patients diagnosed with CAP who actually have coccidioidomycosis. This investigation will provide more information about testing practices, empiric treatment practices, and follow-up of patients with coccidioidomycosis. Lastly, ADHS will begin enhanced surveillance for coccidioidomycosis to further characterize risk factors and clinical outcomes so that public health interventions can be developed. These efforts will enable ADHS to develop public health interventions to control coccidioidomycosis in Arizona and to increase the knowledge about the natural history of the disease to prepare for a potential bioterrorism event involving this select agent.

[*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.]

ACKNOWLEDGMENT

The authors acknowledge Jamie Kokko for her technical assistance with manuscript preparation.

REFERENCES

1. Galgiani, J.N., N.M. Ampel, J.E. Blair, *et al*. 2005. Coccidioidomycosis. Clin. Infect. Dis. **41:** 1217–1223.

2. CENTERS FOR DISEASE CONTROL AND PREVENTION. 2004. Summary of Notifiable Diseases—United States—2004. Published June 16, 2006, for Morb. Mortal. Wkly. Rep. 53 (No 53).
3. AMPEL, N.M., D.G. MOSLEY, B. ENGLAND, *et al*. 1998. Coccidioidomycosis in Arizona: increase in incidence from 1990 to 1995. Clin. Infect. Dis. **27:** 1528–1530.
4. EINSTEIN, H.E. & R.H. JOHNSON. 1993. Coccidioidomycosis: new aspects of epidemiology and therapy. Clin. Infect. Dis. **16:** 349–356.
5. VALDIVIA, L., D. NIX, M. WRIGHT, *et al*. 2006. Coccidioidomycosis as a common cause of community acquired pneumonia. Emerg. Infect. Dis. **12:** 958–962.
6. CHANG, D.C., B.J. PARK, L.A. BURWELL, *et al*. 2006. Disparities in testing practices for *Coccidioides* among patients with community-acquired pneumonia—Metropolitan Phoenix, 2003–2004. Poster [M-1608]; 46th Interscience Conference on Antimicrobial Agents and Chemotherapy; Sep 27–30, San Francisco, CA.
7. PAPPAGIANIS, D. 1994. Marked increase in cases of coccidioidomycosis in California: 1991, 1992, and 1993. Clin. Infect. Dis. **19**(Suppl 1):S14–S18.
8. SMITH, C.E., R.R. BEARD, H.G. ROSENBERGER & E.G. WHITING. 1946. Effect of season and dust control on coccidioidomycosis. JAMA **132:** 833–338.
9. PAPPAGIANIS, D. 1988. Epidemiology of coccidioidomycosis. Curr. Top. Med. Mycol. **2:** 199–238.
10. KOLIVRAS, K.N. & A.C. COMRIE. 2003. Modeling valley fever (coccidioidomycosis) incidence on the basis of climate conditions. Int. J. Biometeorol. **47:** 87–101.
11. PAPPAGIANIS, D. & H. EINSTEIN. 1978. Tempest from Tehachapi takes toll or *Coccidioides* conveyed aloft and afar. West J. Med. **129:** 527–530.
12. MANT, J., S. WILSON, J. PARRY, *et al*. 2006. Clinicians didn't reliably distinguish between different causes of cardiac death using case histories. J. Clin. Epidemiol. **59:** 862–867.
13. RODRIGUEZ, S.R., S. MALLONEE, P. ARCHER & J. GOFTON. 2006. Evaluation of death certificate-based surveillance for traumatic brain injury–Oklahoma 2002. Public Health Rep. **121:** 282–289.