Coccidioidomycosis in Tulare County, California, 1991: reemergence of an endemic disease

E. DURRY,* D. PAPPAGIANIS,† S. B. WERNER,‡ L. HUTWAGNER,* R. K. SUN,§ M. MAURER§, M. M. McNEIL* & R.W. PINNER*

*Division of Bacterial and Mycotic Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia 30333; †Department of Medical Microbiology and Immunology, University of California, Davis, CA 95616; ‡State Department of Health Services, Sacramento, CA 95814; and §Tulare County Health Department, Tulare, CA 93274, USA

In 1991, 1208 cases of coccidioidomycosis were reported to the California Department of Health Services, compared with an annual average of 450 during 1986-90. We conducted a study in Tulare County to define the epidemiology of the disease and identify risk factors for severe disease, focusing on the epidemic period September 1991–December 1991. To identify cases, we used data from the Coccidioidomycosis Serology Laboratory at the University of California, Davis, other laboratories, and the Tulare County Health Department’s coccidioidomycosis reporting system. We compared patients who were hospitalized with those who were not to determine risk factors for severe disease. We identified 128 cases of acute coccidioidomycosis diagnosed between 1 September and 31 December 1991 (attack rate 41/100,000); south central Tulare County had the highest attack rate. Thirty-five (27%) case-patients were hospitalized. Male sex (relative risk (RR) 2.5, 95% confidence interval (CI) 1.2–5.0), black people and Asian races (RR 4.8, 95% CI 2.4–9.6), and age ≥20 years (RR 8.3, 95% CI 1.2–57.4) were univariately significant and remained independently associated with hospitalization in multivariate analysis. The 1991 Tulare County outbreak of coccidioidomycosis was part of a much larger outbreak that began in California during 1991 and continued through 1993. The outbreak was preceded by an unusually rainy spring. Although dust reduction measures during times of increased coccidioidomycosis incidence can help reduce exposure, definitive control awaits the development of a safe, effective vaccine.

Keywords coccidioidomycosis, Tulare County

Introduction

Between 1991 and 1994, California experienced its highest reported incidence of coccidioidomycosis. In 1991, 1200 new cases of coccidioidomycosis were reported to the California Department of Health Services, compared with a yearly average of 450 cases in the previous 5 years. In 1992, the number of reported cases increased to more than 4516, an increase which was sustained during 1993 when 4137 cases were reported [1,2]. The vast majority of cases was reported from counties in the San Joaquin Valley; 76% of the cases during 1992 was reported from Kern and Tulare counties, in the heart of an area of endemic coccidioidomycosis in California. Over 50 years ago, Smith’s studies of valley fever in Tulare and Kern counties laid the foundation for understanding the epidemiology of this disease [3–5] while these recent events underscore how dynamic factors such as demographic and environmental changes can affect the emergence and re-emergence of infectious diseases [6]. In this paper, we extend Smith’s findings and describe a recent outbreak in Tulare County that identifies risk factors for severe disease.
Methods

Epidemiology of coccidioidomycosis in Tulare County, 1990–91

In Tulare County, physicians refer virtually all serum specimens for the diagnosis of coccidioidomycosis to the Coccidioidomycosis Serology Laboratory, University of California, Davis (UCD). To describe the epidemiology of coccidioidomycosis in Tulare County we used data from cases newly diagnosed in the UCD laboratory by any positive result of the IDTP immunodiffusion test for evidence of infection (i.e. tests for IgM or IgG) with *Coccidioides immitis* [7].

![Graph](image)

**Fig. 1** Coccidioidomycosis cases in Tulare County, California, diagnosed at the University of California, Davis, 1990–91.

Analysis of meteorological data

The California Department of Water Resources provided meteorologic data through the California Irrigation Management Information System (CIMIS). We used Winter’s method to forecast monthly total precipitation, average maximum daily temperature, and average daily wind run for Tulare County in 1991, based on actual meteorologic data from the years 1983–90. Then, we compared the forecasted values with actual 1991 meteorological data [10].

Results

Epidemiology of coccidioidomycosis in Tulare County, 1990–91

During 1991, 202 cases of coccidioidomycosis (positive IgM or IgG) were newly diagnosed at the UCD laboratory, compared with 81 during 1990 (Fig. 1). Of the 202 cases, 141 (70%) were diagnosed during the months of September to December.

Risk factors for severe coccidioidomycosis

We used hospitalization as an indicator of disease severity and compared potential risk factors in hospitalized vs non-hospitalized patients. We also compared patients with radiological findings indicating severe primary pulmonary coccidioidomycosis with those whose radiographs did not show such findings. Chest radiograph evidence of multiple pulmonary infiltrates, cavitary lesions or pleural effusions were considered indicators of severe primary pulmonary disease.

We used the $\chi^2$ test to evaluate the statistical significance of the distribution of discrete variables, and Mantel-Haenszel estimates of relative risk using 95% confidence intervals. We analysed data with ‘Epi Info’ and SAS statistical software packages [8,9].
### Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases</th>
<th>Attack rate per 100,000</th>
<th>Hospitalized No. (%)</th>
<th>RR for hospitalization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>128</td>
<td>41</td>
<td>35 (27)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>54</td>
<td>35</td>
<td>8 (15)</td>
<td>1 (Reference)</td>
</tr>
<tr>
<td>Male</td>
<td>74</td>
<td>48</td>
<td>27 (37)</td>
<td>2.5 (1.2-5.0)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 20</td>
<td>25</td>
<td>22</td>
<td>1 (4)</td>
<td>1 (Reference)</td>
</tr>
<tr>
<td>≥ 20</td>
<td>103</td>
<td>52</td>
<td>34 (33)</td>
<td>8.3 (1.2-57.4)</td>
</tr>
<tr>
<td>Race*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>62</td>
<td>36</td>
<td>9 (15)</td>
<td>1 (Reference)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>42</td>
<td>37</td>
<td>12 (29)</td>
<td>2.0 (0.9-4.3)</td>
</tr>
<tr>
<td>Black</td>
<td>2</td>
<td>48</td>
<td>2 (100)</td>
<td>6.9 (3.8-12.6)</td>
</tr>
<tr>
<td>Asian</td>
<td>11</td>
<td>153</td>
<td>7 (64)</td>
<td>4.4 (2.1-9.3)</td>
</tr>
<tr>
<td>Other</td>
<td>7</td>
<td>42</td>
<td>5 (71)</td>
<td>4.9 (2.3-10.6)</td>
</tr>
</tbody>
</table>

*Information available on 124 patients.

Among all other races (95% CI 3.0-4.7). Among 111 patients for whom information on duration of residency in the San Joaquin Valley was available, 59 had moved to the valley from areas where coccidioidomycosis is not endemic. None of the 11 Asians were life-long residents of the valley, compared with 38 (38%) of others from whom this information was available (P < 0.001).

The attack rate varied significantly by geographic area within the county (P < 0.001). Residents of three contiguous cities in the foothills of the Sierra Nevada in south central Tulare County had attack rates higher than 110 per 100,000, compared with less than 65 per 100,000 for other cities in the county (Fig. 2). Residents of these cities were 4.4 times as likely as residents of other areas to have coccidioidomycosis (95% CI 2.4-8.1). Stratified analysis showed that area of residency did not explain the higher attack rate among Asians.

### Clinical manifestations

Fever, cough, fatigue, malaise, pleuritic chest pain and musculoskeletal symptoms occurred in over half the case-patients (Table 2).

Erythema nodosum occurred in 34 (72%) patients. Univariate analyses demonstrated that erythema nodosum occurred more frequently in females (RR 8.1, 95% CI 3.4-19.4) and in those younger than 20 years of age (RR 3.5, 95% CI 2.1-5.7). By stratified analysis, female sex and age younger than 20 years were independently associated with erythema nodosum. The occurrence of erythema nodosum was not associated with race.

Thirty-five patients (27%) were admitted to a hospital. Thirty patients had severe primary pulmonary coccidioidomycosis, and five had disseminated disease. Three of the disseminated cases occurred in Filipinos and two in Hispanics. The site of dissemination was the central nervous system in three patients and the skin in two patients.

There were four (3%) deaths. One Mexican and one Asian patient died because of central nervous system dissemination. Two other patients, both black people, died from severe pulmonary disease without evidence...
of dissemination; one of the patients had a congenital heart defect complicated by chronic heart failure.

Risk factors for hospitalization

The risk of hospitalization varied significantly by sex, age and race. Males were 2.5 (95% CI 1.2–5.0) times as likely to be hospitalized than were females (Table 1). The mean age of patients with coccidioidomycosis was 43 years for those who were hospitalized and 34 years for those who were not. Only one hospitalized case occurred in a person younger than 20 years old. Those 20 years old or older were 8.3 (CI 1.2–57.4) times as likely to be hospitalized than were white people. Together, black people and Asians were 4.8 (95% CI 2.4–9.6) times as likely as non-Hispanic whites to be hospitalized. Male sex, black people and Asian races remained independently associated with hospitalization in multivariate analysis.

Chest radiographs indicated severe primary pulmonary coccidioidomycosis in 29 (23%) patients, of whom 24 (83%) were hospitalized. Only 11 (11%) patients without such chest radiograph findings were hospitalized. Stratified analysis showed no difference in the rates of hospitalization by race or sex.

None of the 33 patients with erythema nodosum were admitted to the hospital or had a chest radiograph suggesting severe primary pulmonary coccidioidomycosis.

Analysis of meteorologic data

During March 1991, rainfall totalled 7.6 inches, compared with an average of 1.6 inches during March of the previous 8 years (Fig. 3). Rainfall during March 1991 exceeded the upper 95% confidence limit of the forecasted range for March or any other month, based in 1983-90 rainfall data. Actual rainfall for the late spring and summer of 1991 was lower than forecasted. There were no significant differences between forecasted and actual rainfall for any other months. There were no significant differences for any month between forecasted and actual values of average maximum daily temperature or average daily wind run. Figure 4 shows that the outbreak began after heavy March rains were followed by a typically windy and dry summer.

Discussion

This outbreak in Tulare County occurred as part of a much larger outbreak that began in California during 1991 and continued through 1993 [11]. Focusing on this county, where the vast majority of cases were diagnosed at a single laboratory, facilitated case ascertainment. The number of coccidioidomycosis infections that actually occurred in the county was undoubtedly much higher than the number detected. This is because approximately 60% of coccidioidomycosis infections are asymptomatic, persons with milder cases may not seek medical care, and those who do may not have serum obtained for diagnostic tests.

The outbreak probably resulted from a combination of circumstances: weather changes, demographics and geography, which illustrate how a variety of factors can combine to augment the emergence of infectious diseases [6]. Weather data showed that rainfall in the spring before the outbreak began was unusually heavy. This supports the long held view that heavy spring rains may enhance the growth of C. immitis and result in more infections during the drier, windier summer and fall. Moreover, the increased rain in the spring of 1991 followed several years of relative drought. This observation supports the hypothesis of some experts that during times of

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relative drought, \textit{C. immitis} may survive better in the soil than its competitors, ‘blooming’ when the rain comes [12-14].

Demographic factors probably also played a substantial role in this outbreak. Skin test surveys conducted during the 1950s among military recruits found approximately 70% skin test positivity among recruits who were life-long residents of areas where coccidioidomycosis is highly endemic. However, the prevalence of skin test positivity among Tulare County residents may have been substantially lower before this outbreak. The population of California increased 49% from 1970 to 1990; many of those who only recently moved to coccidioidomycosis endemic counties were probably previously unexposed to \textit{C. immitis} and therefore susceptible. In addition, topographical changes, such as paved roads and well-maintained lawns, probably decreased exposure to \textit{C. immitis} over the past several decades, also increasing the proportion of susceptible persons.

The highest attack rates were concentrated in the south central portion of Tulare County. It is possible that recent land development and construction projects might have contributed to the particularly high attack rates in the south central area of the county. Interestingly, however, this same part of the county apparently also experienced the highest attack rates during Smith’s studies between 1937 and 1939 [3]. These observations, more than 50 years apart, suggest that levels of risk for coccidioidomycosis vary by locale even within recognized endemic areas.

Previous studies have generally not shown racial differences in acquiring \textit{C. immitis} infection [4,15,16]. The most likely explanation for the higher attack rate among Asians in this study is their recent immigration from non-endemic areas. Numerous previous studies have found, however, an increased risk of disseminated coccidioidomycosis among certain demographic groups, including black people, Hispanics, Asians and males [4,15,17,18].

We identified black people and Asian race, male sex and age over 20 years as risk factors for severe coccidioidomycosis as evidenced by hospitalization for disseminated disease or severe primary pulmonary coccidioidomycosis. This association of race and sex with severe primary as well as disseminated coccidioidomycosis has been observed but not widely recognized previously. For example, in a review of autopsy records from five California counties, Huntington found coccidioidomycosis pneumonia as a cause of death in a disproportionately high number of black people. [19]. Although Smith found a comparable proportion of asymptomatic infections in black and white peoples, symptomatic infections were more likely to be recognized in black people, perhaps indicating a tendency toward more severe symptoms [4]. Lundergan and colleagues found chest radiographs to be abnormal for 61% of males but for only 47% of females among students with coccidioidomycosis diagnosed at the Student Health Services at the University of Arizona between 1979 and 1983, suggesting more severe primary illness among males [20].

There are no clear explanations for the consistent findings of differences by race and sex in the occurrence of severe coccidioidomycosis. Although several investigators have suggested that differences in exposure and socioeconomic status cannot alone explain these race and sex differences, future studies should pay more careful attention to these factors and should begin to assess possible genetic and hormonal factors as well [4,16,21].

The predilection of erythema nodosum for females and its association with milder \textit{C. immitis} infection was described by Smith and others [3,4,15,22]. Smith did not estimate an age-specific risk for the development of erythema nodosum in those infected with \textit{C. immitis}, although his data did suggest that erythema nodosum was associated with younger ages [4]. Our study found a significant association of age less than 20 with the occurrence of erythema nodosum, independent of sex.

Formulating public health strategy to prevent or control coccidioidomycosis poses difficult challenges. Additional epidemiological studies could clarify and quantify risks of infection with \textit{C. immitis} as well as the risk of severe disease among those who become infected. It is not clear whether reducing the level of exposure to \textit{C. immitis} reduces the severity of disease or the likelihood of symptomatic infection. During World War II, Smith et al. demonstrated that dust reduction reduced infections among personnel at Army air fields in the San Joaquin Valley [5]. For short-term exposures, then, efforts to reduce exposure to dust in areas of endemic coccidioidomycosis can reduce infection risk. The benefits of dust reduction measures are less clear for long-term residents of such areas, who are likely to be exposed to the fungus at some time during their lives. Smith et al. reported that 60% of \textit{C. immitis} infections are asymptomatic [4]. However, during outbreaks, when exposures are probably particularly intense, reported attack rates of symptomatic coccidioidomycosis have tended to be higher, reaching as high as 77% [23]. This observation suggests that dust reduction measures might be effective, even for long-time residents, in keeping symptomatic infections to a minimum.

Recovery from natural infection with \textit{C. immitis} tends to confer lasting protection from reinfection, which suggests that vaccination should be an effective prevention strategy. However, while coccidioidomycosis vaccines have been successful in experimental animals, a recent trial in humans of a vaccine consisting of killed intact spherules failed to demonstrate efficacy [24].
Modern genetic and biochemical methods offer promise that candidate antigens for a coccidioidomycosis vaccine could be identified and produced. As it is impossible to eliminate totally exposure to the organism in areas of endemic coccidioidomycosis, vaccination probably offers the best hope for effective prevention.

Acknowledgements

Use of trade names and commercial sources is for identification only and does not imply endorsement by the US Public Health Service or the US Department of Health and Human Services.

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