MAJOR ARTICLE

An Epidemic of Coccidioidomycosis in Arizona Associated with Climatic Changes, 1998–2001

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Background. Reports of coccidioidomycosis cases in Arizona have increased substantially. We investigated factors associated with the increase.

Methods. We analyzed the National Electronic Telecommunications System for Surveillance (NETSS) data from 1998 to 2001 and used Geographic Information Systems (GIS) to map high-incidence areas in Maricopa County. Poisson regression analysis was performed to assess the effect of climatic and environmental factors on the number of monthly cases; a model was developed and tested to predict outbreaks.

Results. The overall incidence in 2001 was 43 cases/100,000 population, a significant ($P < .01$, test for trend) increase from 1998 (33 cases/100,000 population); the highest age-specific rate was in persons ⩾65 years old (79 cases/100,000 population in 2001). Analysis of NETSS data by season indicated high-incidence periods during the winter (November–February). GIS analysis showed that the highest-incidence areas were in the periphery of Phoenix. Multivariable Poisson regression modeling revealed that a combination of certain climatic and environmental factors were highly correlated with seasonal outbreaks ($R^2 = 0.75$).

Conclusions. Coccidioidomycosis in Arizona has increased. Its incidence is driven by seasonal outbreaks associated with environmental and climatic changes. Our study may allow public-health officials to predict seasonal outbreaks in Arizona and to alert the public and physicians early, so that appropriate preventive measures can be implemented.

Coccidioidomycosis is caused by *Coccidioides* species (*C. immitis* and *C. posadasii*). Clinical manifestations can range from self-limited, community-acquired pneumonia to disseminated infection that can involve the central nervous system, skin, bones, joints, and other organs throughout the body [1, 2]. Approximately 60% of infected persons are asymptomatic [3, 4]. Infection by *Coccidioides* species can follow inhalation of the fungal arthrospores, which exist in the soil of endemic areas [5]. Endemic areas include Mexico, parts of Central and South America, and the southwestern United States, particularly the desert areas of Maricopa, Pinal, and Pima Counties in Arizona and Kern, Tulare, and Fresno Counties in California [6–9].

Outbreaks of coccidioidomycosis have been associated with soil disruption, archaeological digs, construction, and even earthquakes [10–13]. In endemic areas, coccidioidomycosis has been linked to climatic conditions. Previous studies have postulated that *Coccidioides* species arthrospores are most abundant in the soil after heavy rains and may be most effectively dispersed during dry, hot periods, such as prolonged droughts [1, 10, 14]. Incidence in California is thought to be seasonal, with peak incidence occurring during the winter months [15]. Studies of specific groups have suggested that seasonal disease occurs in Arizona, although this has not been shown by use of state surveillance data [16, 17].

Surveillance of coccidioidomycosis in Arizona before 1995 was based on voluntary physician reporting and

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was done only at the state level [18]. In 1995, a clear case definition for coccidioidomycosis, incorporating laboratory confirmation, was adopted by the Council of State and Territorial Epidemiologists [19]. At this time, it was made a nationally notifiable disease at the southwest regional level. The annual incidence of coccidioidomycosis in 1995 was estimated to be 15 cases/100,000 population [18].

In 1997, the state of Arizona made coccidioidomycosis a mandatory reportable disease for laboratories, and, as a result, reporting of coccidioidomycosis increased dramatically [18]. Initially, this increase was presumed to be a result of improved reporting (K.K., personal communication); however, incidence continued to increase. In 2001, 2203 cases were reported to the Arizona Department of Health Services (ADHS). We conducted an investigation to better describe the populations affected by the epidemic and to determine which host or environmental factors were associated with the increase.

METHODS

Description of the epidemic. To determine the incidence of disease and hospitalizations related to coccidioidomycosis, we analyzed the National Electronic Telecommunications System for Surveillance (NETSS) data and the Arizona Hospital Discharge Database for 1998–2001. An incident case was defined by use of the NETSS case definition, which requires the presence of clinical and laboratory criteria [19]. These criteria included the presence of cultural, histopathologic, or molecular evidence of *Coccidiodes* species or a serological test result positive for coccidioidal antibodies in serum or cerebrospinal fluid, as determined by (1) detection of coccidioidal IgM by immunodiffusion, EIA, latex agglutination, or tube precipitin or (2) detection of an increasing titer of coccidioidal IgG by immunodiffusion, EIA, or complement fixation. Not all cases were tested by use of all methods. Hospitalizations were identified in the Arizona Hospital Discharge Database by use of *International Classification of Diseases, 9th Revision* codes for coccidioidomycosis (114.0–114.3 and 114.5–114.9). Only incident hospitalizations were included, to avoid counting readmissions for chronic complications related to coccidioidomycosis. Direct hospital charges were totaled by use of the numbers reported in the database.

Denominators for rate calculations were obtained from the 2000 US Census and included estimates for noncensus years. Since accurate census counts of the transient winter population have not been performed, to account for this population, we adjusted denominators using population estimates from previous studies. By use of these data, we estimated an annual statewide winter migration of 300,000 visitors between the months of December and March [20]. Analysis was performed by use of Microsoft Excel 2000 and Epi Info (version 6.02; Centers for Disease Control and Prevention).

To describe the geographic areas of high incidence of disease, we used Geographic Information Systems (GIS) to analyze the Phoenix metropolitan area (Maricopa County), where most case patients resided. Residences of incident case patients were mapped by use of addresses entered in the NETSS database. Boundaries within Maricopa County were defined by use of US Postal Service zip codes, and population estimates from the 2000 US Census were used as denominators, to calculate zip code–specific rates. These rates were age adjusted to the 2000 US Census standard population, to account for geographic differences in elderly populations in Maricopa County. GIS analysis was performed by use of ArcView 3.2 (ESRI).

Determination of factors associated with the increase. To help explain the factors associated with the increase, 2 separate studies were performed. First, we performed a cohort study of case patients, to evaluate whether differences in recalled exposures or host factors were associated with either periods of high incidence or periods of low incidence. We randomly selected case patients from the NETSS database on the basis of whether their disease occurred during a period of high or low incidence. We calculated the minimum sample size to detect a 20% difference in exposures with 80% power and a 95% confidence level, which estimated a total sample size of 180. Phone numbers were available for ~50% of case patients in the NETSS database; we attempted to obtain unavailable phone numbers using the local telephone directory and the Internet (http://www.whitepages.com). Trained personnel conducted phone surveys over the course of 5 days, including evenings and weekends, and asked questions about comorbidities, exposures, diagnosis, and outcome. Data were recorded on standard data-collection forms and were entered into Microsoft Access. The cohort was analyzed according to inclusion in high-incidence and low-incidence groups, to evaluate which factors were statistically more prevalent among case patients during the periods of high incidence. Univariate analysis and multivariable analysis were conducted by use of SAS (version 8.2; SAS Institute).

Next, we conducted a climatologic study to help determine whether changes in environmental or climatic conditions were associated with the increase. Using Poisson regression analysis, we determined the association between the number of monthly cases reported in Maricopa County through NETSS and monthly environmental and climatologic factors. Information on rainfall, drought indices, wind speed, and temperature was obtained from the National Climatic Data Center (Asheville, NC). Dust measurements were obtained from the Maricopa County Department of Environmental Quality. Environmental and climatic variables were chosen on the basis of plausibility of contribution to fungal growth or dissemination. To determine the significance of a recent short drought, we created variables that incorporated the amount of rain that fell recently (within 1 or 2 months) divided by the amount that fell over a longer period (6 or 7 months). Because the exact relationship between climate, environment,

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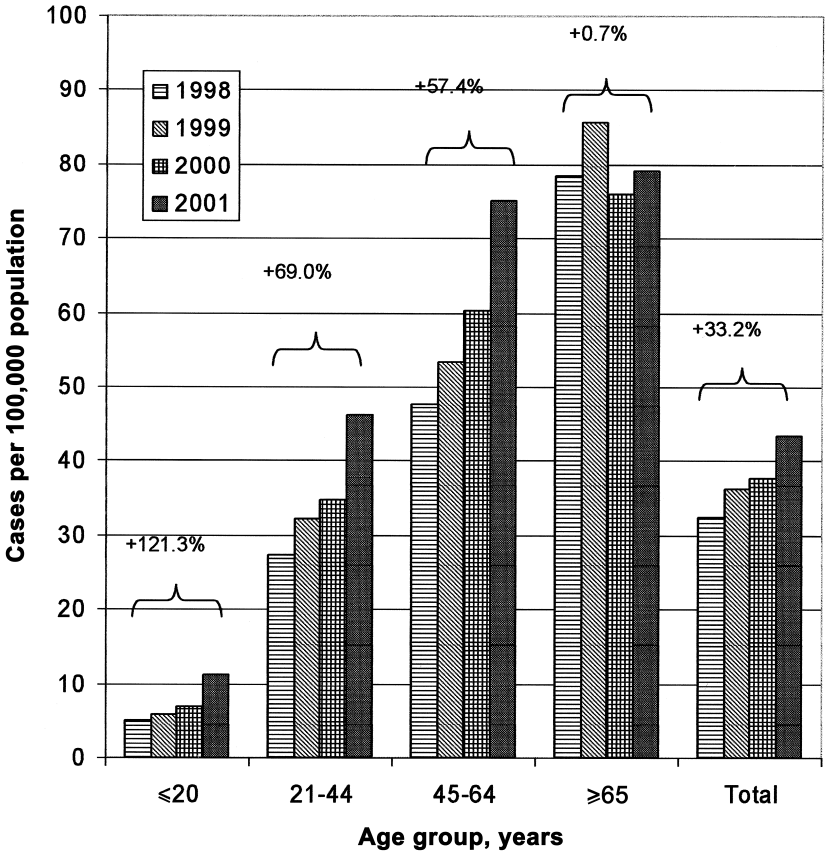

Figure 1. Incidence of coccidioidomycosis in Arizona, by year and age group. The percentages indicate the proportional increase in incidence of disease between 1998 and 2001.

and disease has not been determined, we evaluated numerous such variables by univariate analysis. Variables were time lagged by 1 month to account for the time between exposure and onset of illness. Variables significant in the univariate analysis were included in a multivariable Poisson regression model. Multiple models were created and tested for the ability to reproduce actual monthly cases. Interactions between significant variables were assessed, and correlation of variables, to evaluate for colinearity, was performed. A final model was chosen on the basis of a high R^2 value, few interactions, and low colinearity. Poisson regression analysis was conducted by use of SAS.

RESULTS

Description of the Epidemic

Overall, 7599 total cases were reported to the ADHS during 1998–2001. The majority of case patients were from Maricopa County (5399; 72% of total); 1391 case patients (19%) were from Pima County (Tucson metropolitan area). The median age was 52 years, and 58% were males. Of the 2239 case patients (29%) for whom reported data on race were available, 81% were white, 5% were African American, and 14% were Hispanic.

The annual incidence of coccidioidomycosis in Arizona increased from 33 cases/100,000 population in 1998 to 43 cases/100,000 population in 2001 ($P<.001$, test for trend). Persons ≥65 years old had the highest overall incidence (79 cases/100,000 population in 2001), although the greatest increases during the study period were seen in younger patients (figure 1). The 12-month composite incidence displayed a seasonal pattern, with peaks occurring from November to February of each year (figure 2). This pattern persisted after adjustment of the denominator for an estimate of the increased winter population.

Hospitalizations also increased throughout the study period; 69 patients (1.4/100,000 population) were hospitalized during 1998 with a new diagnosis of coccidioidomycosis, and 598 (11.8/100,000 population) were hospitalized during 2001 ($P<.001$, test for trend). Persons ≥65 years old composed 34% of all hospitalized patients during the study period and had the highest rate of hospitalization—29/100,000 population in 2001. Overall, 26% of hospitalized patients had disseminated disease, including 10% with coccidioidal meningitis. Direct hospital charges for patients who had received primary or secondary diagnoses of coccidioidomycosis increased from $2,079,236 in 1998 to $19,342,776 in 2001. Hospital charges for the 1998–2001 period totaled $33,154,571 ($33,762/hospitalized patient).

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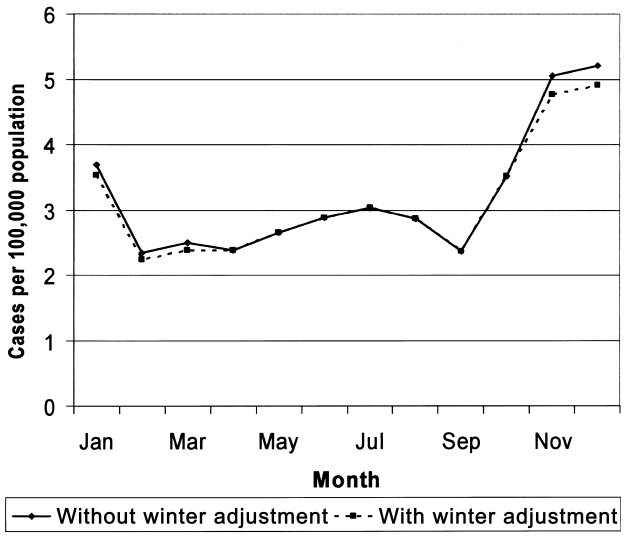

Figure 2. Twelve-month composite incidence of coccidioidomycosis in Arizona during 1998–2001. Periods of high incidence were seen during the winter seasons (October–February). Adjustment of the denominator for an increase in seasonal winter visitors *(dotted line)* did not substantially change the large seasonal peaks.

A map of the incidence in Maricopa County shows a great degree of geographic variation (figure 3). The highest age-adjusted rates were primarily in the periphery of Phoenix (figure 3).

Determination of Factors Associated with the Increase

Cohort study. Of 208 persons contacted by telephone, 196 (94%) agreed to participate. Fifty-five percent were males, and 86% were white. The median age was 63 years. The median time to diagnosis was >4 weeks from the onset of symptoms, and the median time that people felt ill was >2 months. Once the diagnosis of coccidioidomycosis was established, 70% received treatment with an antifungal medication, but 59% also received antibacterial agents at some time during their illness; 46% reported being hospitalized. Prior knowledge of coccidioidomycosis was limited: ~33% of survey participants had not heard of coccidioidomycosis (or its common name, valley fever) before diagnosis. Persons of nonwhite race were more likely to not have heard about coccidioidomycosis before diagnosis (relative risk [RR], 1.8 [95% confidence interval {CI}, 1.03–3.07]; $P = .01$), and patients with a lack of knowledge about coccidioidomycosis were more likely to have received a diagnosis of coccidioidomycosis >2 weeks after the onset of symptoms (91% vs. 72%; RR, 1.2 [95% CI, 1.1–1.5]; $P = .01$).

Known risk factors for coccidioidomycosis were not statistically more prevalent during the periods of high incidence than during the periods of low incidence. For example, living for <1 year in Arizona was reported by 10% of case patients infected during periods of high incidence, compared with 14% of case patients infected during periods of low incidence ($P = .5$). Other variables not statistically significant included being in a dust storm during the month before illness (30% vs. 28%; $P = .8$), having diabetes (18% vs. 17%; $P = .8$), having a condition or taking medication resulting in immunosuppression (8% vs. 10%; $P = .6$), and being a smoker at the time of illness (21% vs. 22%; $P = .8$). As we were unable to find any variables significant at $P < .1$, no multivariable analysis was performed.

Climatologic study. The association between the number of monthly cases of coccidioidomycosis in Maricopa County and selected climatic and environmental variables is shown in table 1. Statistically significant climatic and environmental variables included drought indices (Palmer Z Index and Palmer Drought Severity Index), wind, mean temperature, dust (measured by concentration of suspended particulate matter <10 μm), and rainfall (table 1).

Significant variables were included in a multivariable Poisson regression model. The final model had an R^2 value of 0.75 and included cumulative rainfall during the previous 7 months, the average temperature during the previous 3 months, dust during the previous month, and the proportion of rainfall during the previous 2 months divided by rainfall during the previous 7 months. The distribution of the modeled cases compared with that of the reported cases in Maricopa County is shown in figure 4. The modeled curve reproduces the peak seasonal periods seen in 1998 and 1999 and accurately reflects the large peak beginning in November 2001. The model also accurately describes an absence of a seasonal peak starting in November 2000, although it incorrectly predicts a peak in September 2000.

DISCUSSION

Coccidioidomycosis has been causing increasing morbidity in Arizona, and the related public-health burden to the state of Arizona is considerable: it is currently the fourth most commonly reported condition to the ADHS; only gonorrhea, chlamydia, and chronic hepatitis C are reported more frequently (K.K., personal communication). The present study has described an epidemic of coccidioidomycosis in Arizona that has been driven by seasonal peaks in incidence associated with climatic changes.

Although coccidioidomycosis has previously been described as having a seasonal pattern in select groups, the present study is the first statewide report of this pattern. Mandatory laboratory reporting in 1997 improved the timeliness and completeness of the surveillance system and probably helped to reveal the seasonal pattern. These seasonal outbreaks do not seem to be related to changes in population characteristics, exposures, or comorbidities. Adjusting for the yearly winter migration of elderly persons did not account for the outbreaks. Similarly, we found no exposure differences between case pa-

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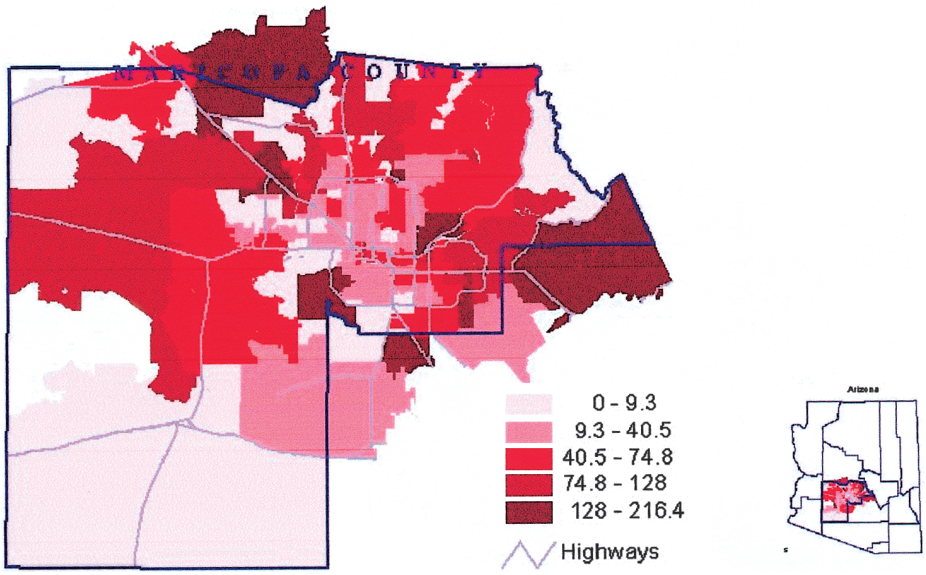

Figure 3. Average annual incidence of coccidioidomycosis in Maricopa County, Arizona, by postal zip code, during 1998–2001. Rates were age adjusted to the 2000 US Census standard population, to account for the geographic differences in age distribution.

tients during periods of high incidence and case patients during periods of low incidence that could explain the seasonal peaks.

GIS analysis identified high age-adjusted rates in areas undergoing high rates of construction activity and development around the periphery of metropolitan Phoenix. However, in the Poisson regression model, the number of monthly building permits issued was not statistically associated with incidence of disease. This is likely because the timing of building-permit issuance does not correlate with the time of the actual construction and digging. Although the present study has suggested a relationship between high incidence of disease and areas with high rates of construction, further risk-factor studies should be performed to thoroughly address this relationship. For example, persons who live in or move to areas with high rates of construction and development may not have had prior exposure to *Coccidioides* species and may subsequently be at higher risk for disease. Another potential explanation for this geographic distribution is that some of these areas also have large retirement communities with a potentially immunonaive population. Although the rates have been age adjusted to account for differences in distribution of the elderly population, these areas may also have high rates because of a large proportion of recent migrants to the region.

Climatic variables describing hot, dry conditions had the strongest association with incidence. A Poisson regression model successfully recreated the observed seasonality during 1998–2001, including the large peak beginning in November 2001. Although the model correctly did not predict a peak during the winter of 2000, it incorrectly predicted a small peak in September 2000. This incorrect prediction is likely a reflection of the complicated relationship between climate and disease and underlines the need for future studies to refine the interaction between these factors.

Other models have found similar relationships between coccidioidomycosis and climate [14, 21]. One model, which incorporated data from California, found that length of drought and mean annual rainfall during the current year were the most predictive of cases, with an R^2 value of 0.45. However, this model relied on old surveillance data starting from 1956. In addition, it tested yearly incidence changes and did not explain seasonal variation. The model developed in the present study uses current surveillance data and real-time predictors and accurately describes 75% of the monthly fluctuations seen.

An important component of the epidemic in Arizona is the large burden of disease in older populations. Persons ⩾65 years old had the highest rate of disease and hospitalization related to coccidioidomycosis. Given the continued migration of such persons to the area, this population is likely to continue to be highly affected. However, we found that the incidence in younger populations is increasing, particularly in those 0–18 years old. Physicians should be aware of this emerging infection in patients of all age groups who are living in or who have traveled to an endemic area.

Although the cohort study did not identify host factors or exposures that were associated with the periods of high incidence, it nonetheless highlighted some important aspects of the epidemic in Arizona. Median time to diagnosis was long (>4 weeks), and many patients had not heard of coccidioidomycosis before their illness. Additionally, the cohort study identified that nonwhites were more likely to not have heard about coccidioidomycosis before becoming ill, and, therefore, they may

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Table 1. Association between selected monthly environmental and climatic variables and total monthly cases of coccidioidomycosis in Maricopa County, during 1998–2001, by Poisson regression analysis.

Parameter	RR (95% CI)	*P*
No. of building permits issued	1.0 (1.0–1.0)	.43
Palmer Z Index	0.921 (0.874–0.970)	.002
PDSI	0.939 (0.897–0.983)	.007
Average wind velocity	0.835 (0.728–0.957)	.009
Average wind velocity during previous 2 months	0.965 (0.858–1.086)	.55
Average temperature during previous 3 months[a]	1.012 (1.003–1.020)	.009
Average dust[a]	1.015 (1.007–1.024)	<.001
Rainfall during previous 3 months	0.926 (0.796–1.076)	.31
Cumulative rainfall during previous 2 months/cumulative rainfall during previous 7 months[a]	0.554 (0.331–0.930)	.025
Cumulative rainfall	0.797 (0.681–0.933)	.005
Cumulative rainfall during previous 7 months[a]	0.860 (0.814–0.908)	<.001

NOTE. Risk ratios (RRs) >1.0 were positively associated with the no. of cases during a given month. CI, confidence interval; Palmer Z Index, short-term drought index; PDSI, Palmer Drought Severity Index (a measure of long-term drought severity).

[a] Included in the final model.

be suitable candidates for public-awareness campaigns. These groups may be particularly important to target, since some nonwhites, particularly African Americans and Filipinos, are at increased risk for developing severe or disseminated disease [7].

The present study was subject to some limitations. The cohort study was subject to recall bias, since patients were asked about past exposures and risk factors. However, since all groups had disease, the recall bias of remembering certain exposures should have been equal in all groups. Another limitation of the cohort study was that the phone survey was conducted during October, before many winter visitors had arrived. Therefore, the proportion of winter visitors in the study was probably underrepresented in all groups. The respondents in the cohort were generally older than those in the surveillance group, probably because younger persons are less likely to maintain a phone number. The high proportion of persons who reported being hospitalized is likely a reflection of this.

Preventive measures for coccidioidomycosis may not be readily available, especially if seasonal outbreaks are due to climatic changes. Some measures are currently in place to reduce dust—for example, construction companies often wet the soil before digging, and many dirt roads are being paved. Despite these measures, however, our study has shown that incidence and associated morbidity have been increasing substantially in Arizona. If abnormally hot and dry conditions continue in Arizona, incidence could increase further.

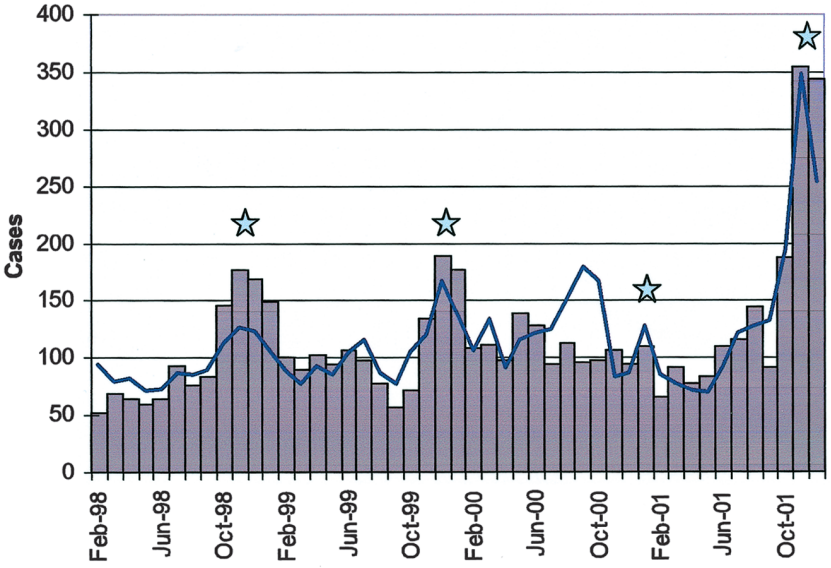

Figure 4. Nos. of actual monthly cases, compared with those predicted by use of a climate-based model, for Maricopa County, Arizona, during 1998–2001. Monthly cases are represented by the solid bars, and predicted cases are represented by the line. Winter peak seasons are marked with stars.

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A vaccine that is currently in development may provide adequate immunity to infection in the future [22–24], but, until such measures for prevention are available, public-health officials should implement measures and programs to increase awareness to improve diagnosis and proper treatment. Identification of climatic patterns that could predispose to epidemics should allow public-health officials to warn physicians about large "cocci seasons," thereby heightening clinical suspicion and leading to more-timely diagnosis and more-appropriate management, avoiding overuse of antibiotics. Such appropriate management may include use of oral antifungals, which may decrease the risk of developing severe pulmonary disease [7]. In addition, susceptible patients, such as the immunocompromised or elderly, may be warned to avoid activities that may potentially put them at higher risk. Future studies should focus on strategies to improve timely diagnosis as well as on methods to prevent severe or disseminated disease.

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