Fluctuations in Climate and Incidence of Coccidioidomycosis in Kern County, California

A Review

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ABSTRACT: Coccidioidomycosis (Valley Fever) is a fungal infection found in the southwestern United States, northern Mexico, and some places in Central and South America. The fungi that cause it (*Coccidioides immitis* and *Coccidioides posadasii*) are normally soil dwelling, but, if disturbed, become airborne and infect the host when their spores are inhaled. It is thus natural to surmise that weather conditions, which foster the growth and dispersal of *Coccidioides,* must have an effect on the number of cases in the endemic areas. This article reviews our attempts to date at quantifying this relationship in Kern County, California (where *C. immitis* is endemic). We have examined the effect on incidence resulting from precipitation, surface temperature, and wind speed. We have performed our studies by means of a simple linear correlation analysis, and by a generalized autoregressive moving average model. Our first analysis suggests that linear correlations between climatic parameters and incidence are weak; our second analysis indicates that incidence can be predicted largely by considering only the previous history of incidence in the county—the inclusion of climate- or weather-related time sequences improves the model only to a relatively minor extent. Our work therefore suggests that incidence fluctuations (about a seasonally varying background value) are related to biological and/or anthropogenic reasons, and not so much to weather or climate anomalies.

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INTRODUCTION

Much is known about the biological, medical, and indeed the epidemiologic aspects of *Coccidiodes immitis* (*C. immitis*) and *Coccidiodes posadasii* (*C. posadasii*), the fungi that cause Valley Fever (coccidioidomycosis) (see, for example, Ref 1 and references therein). *Coccidioides* have a complete life cycle as soil-dwelling organisms, but if they are disturbed and become airborne, they are able to infect a host via the respiratory tract when the fungi spores are inhaled.

Given its wide geographic distribution, it is evident that *Coccidioides* are able to flourish within somewhat varied climatic environments. Endemic areas include[2] the southern part of the San Joaquin Valley in California, southern California, the southern part of Arizona, New Mexico, and Texas, most of northern Mexico, and some areas in Guatemala, Honduras, Venezuela, northeastern Brazil, Argentina, and Paraguay. There are some variations in climate in these areas: for example, the southern San Joaquin Valley gets most of its precipitation in the winter, whereas the southern part of Arizona gets late summer monsoon rains as well as frontal systems in winter.

Conventional wisdom would suggest that climatic fluctuations might affect the rate at which humans become infected.[1] For example, a wetter-than-normal rainy season might help *Coccidioides* bloom; windy spells might facilitate the dispersal of the fungus; hot summers could be anticipated to suppress competing organisms, thus enhancing the survival of *Coccidioides*.[3] Indeed, anecdotal evidence to this effect is well documented in the literature.[4–13]

There have been a number of attempts at demonstrating this connection quantitatively. They can be divided into two groups: (i) in Arizona, where *C. posadasii* is endemic, a strong connection has been reported[13–15] between climatic patterns and coccidioidomycosis incidence, whereas (ii) in Kern County, California, where *C. immitis* is endemic, only a weak connection has been found.[16,17] In this article, we endeavor to give an overview of our work with incidence and weather data in Kern County. For the purpose of comparison, in this article we discuss some salient points in connection to the works pertaining to Arizona and provide a summary of our own work.

ARIZONA: INCIDENCE–WEATHER CORRELATIONS AND MODELS

Kolivras and Comrie[14] found that antecedent precipitation and temperature are moderate climate risk factors for valley fever in Pima County (which includes Tucson). They developed a multivariate model to account for Valley

Fever incidence in a given month based on climate conditions and anomalies in the antecedent 2 years. Their model uses and predicts a metric called the transformed incidence anomaly. This is the monthly incidence anomaly relative to the annual (rather than the climatological, or climatological monthly) mean. The maximum transformed incidence anomalies they reported in Pima County are about 10% and their model predicts up to half of some anomalies. The transformed incidence is insensitive to uniform increases in monthly incidence, which results in an absolute annual increase (e.g., an epidemic), but which does not change the relative contribution of each month to the annual incidence. (In contrast, the 1991–1995 epidemic in Kern County increased interannual and intra-annual variations in incidence by about 10-fold. This appears to be the largest well-documented epidemic on record.)

Komatsu *et al.*[13] performed a Poisson regression in an effort to model monthly (1998–2001) Valley Fever incidence in Maricopa County, which includes Phoenix. They found a large correlation ($R^2 = 0.75$) between incidence and cumulative rain in the preceding 7 months, average temperature during the preceding 3 months, dust during the preceding month, and precipitation in the preceding 2 months in proportion to the preceding 7 months.

Comrie[15] explored the climate–incidence connection (for 1992–2003 Pima County data) using PM_{10} (particulate matter of size less than 10 μm) concentrations as a proxy for *C. posadasii* abundance in the atmosphere, while at the same time accounting for precipitation time series. The rationale for using PM_{10} is clear: soil dust emitted into the atmosphere from endemic regions may carry a proportional concentration of *Coccidioides* spores (size $\sim 2 \times 5$ μm). Comrie devised an exposure-day methodology, which allowed him to estimate the date of exposure adaptively depending on whether the onset, diagnosis, or report date was available for each patient. Using this approach, he identified a bimodal distribution of the monthly incidence data—a pattern that had not been clearly seen in previous analyses. Comrie then grouped the data into seasons and was able to produce a model that predicted closely the observed disease incidence. This model combined the lagged seasonal precipitation, and concurrent seasonal dust and precipitation, and was able to explain 80% of the variance in coccidioidomycosis seasonal incidence data.

KERN COUNTY: INCIDENCE–WEATHER CORRELATIONS AND MODELS

The Kern County seasonal climate was described in detail in Ref. 16. The area receives in the neighborhood of 16.5 cm of rain a year, largely in the winter. Summers are hot and dry—usually reaching 43°C in July, with virtually no precipitation. May and June experience the largest wind speeds-–and average of the order of 3.5 m/sec, with maxima usually less than 15 m/sec, and very rarely exceeding 20 m/sec. Coccidioidomycosis incidence (number of cases per 100,000 population) also has a corresponding yearly cycle, with the number

generally increasing toward the late fall (incidence near 17 per month per 100,000 population), decreasing in the winter, and reaching a minimum in the spring and summer (incidence near 4.7 per month per 100,000 population).

The work on Kern County data so far has searched for a connection between the fluctuations of Valley Fever incidence (about a seasonally varying background) and climate anomalies, that is, we do not endeavor to explain the seasonal behavior of incidence in terms of climate parameters; instead, we try to explain *incidence fluctuations* in terms of *weather anomalies*. Furthermore, we do not seek to explain or model effects of relatively infrequent events, such as the December 1977 dust storm in Kern County,[7] or the Northridge Earthquake of 1994—both of which produced large outbreaks of the disease.[18]

The climatic variables we have investigated in connection with coccidioidomycosis incidence are precipitation, surface temperature, and wind speed (which we take as a proxy for spore abundance in the atmosphere). We present in FIGURE 1 the annual cycle of coccidioidomycosis incidence in Kern County, and some potential climate risk factors. FIGURE 1 was graphed from monthly

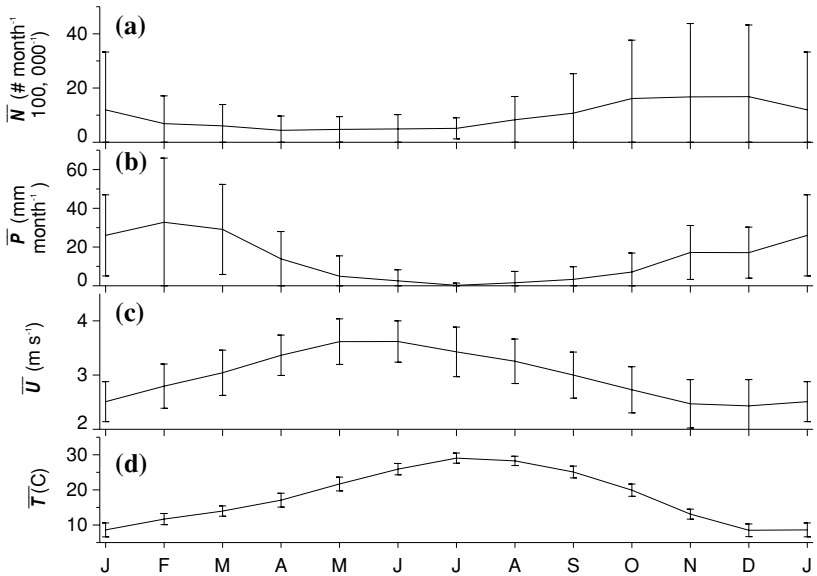

FIGURE 1. Annual cycle of coccidioidomycosis incidence and potential climate risk factors from 1980 to 2002. (**a**) Monthly mean incidence $\bar{N}$ (# per month per 100,000 population), (**b**) precipitation $\bar{P}$ (mm per month), (**c**) wind speed $\bar{U}$ (m per sec), (**d**) surface temperature $\bar{T}$ (C). *Bars*. Two standard deviations of the interannual variability computed separately for each month. Standard deviations computed using 1980–2002 data for incidence, and 1961–2002 for climate variables.

1980–2002 data for incidence and 1961–2002 for climate variables. The bars indicate intramonth variability. Their size was computed as twice the standard deviation for the interannual variability computed separately for each month. We performed a (univariate) lag-correlation analysis between incidence seasonal anomalies on the one hand, and climatic anomalies in each of precipitation, surface temperature, and wind speed on the other hand.[16] We found that only precipitation 8 months prior to incidence had a statistically highly significant correlation with incidence ($P = 0.0020$), but whereas this is consistent with the expectation than an unusually wet winter can lead to larger incidence later in the *Coccidioides* season, the magnitude of the correlation was quite small ($R^2 = 0.04$). Further analysis of bivariate correlations led to inconclusive results. To try to capture nonlinear correlations, we also investigated correlations of incidence anomalies and wind speed anomalies squared and cubed, as well as with wind speeds only within a certain window (from some minimum to some maximum). These efforts also led to no statistically significant correlations.

We used 9 years (Jan 1995–Dec 2003) of weekly mean atmospheric conditions and incidence data to construct a statistical model which allows a degree of prediction.[17] We presented a generalized autoregressive moving average (GARMA) model that maximizes the accuracy of prediction while minimizing the number of input variables.[19] In other words, we maximize the predictive skill of the model while keeping only the most important input parameters, and removing from the input those variables that do not contribute (or contribute minimally) to the prediction task. The method starts from putting into the model parameters that might help predict incidence. We used prior incidence history, as well as precipitation, wind speed, and temperature. As expected (since the number of input parameters is very large), this first step leads to an excellent model. We interpreted this to mean that at least some of the input parameters contain information highly relevant to our prediction task. We called this result the full model (FIG. 2a). The second step entails the minimization procedure mentioned above. We present this result (the final model) in FIGURE 2b. Our most important finding[17] was that the final model does not require any weather parameters—it turned out that in order to predict weekly incidence at some time t, the most important input parameters were weekly incidence at times t-k, where $k = 1, 2, 4, 26$ weeks. We point out that the incidence surges at the end of the period under consideration are predicted by the final model. For comparison, we forced the model to consider the best way to use weather parameters to predict incidence (while not considering information about the history of prior incidence). We called this the environmental model. The result is given in FIGURE 2c. This model predicts only the seasonal variations of incidence (as expected, since weather and incidence have a yearly cycle), but is quite unable to predict the surges in the early 2000s.

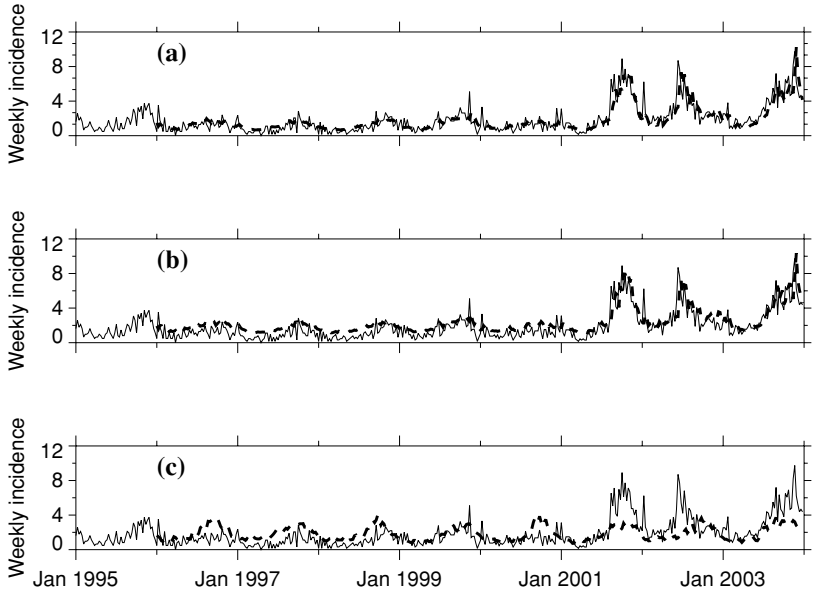

FIGURE 2. Reported Valley Fever incidence in Kern County, California (cases per 100,000 population) and three models for the period Jan 1996–Dec 2003. In all three panels, thin solid lines indicate incidence, and dashed heavy lines correspond to model results: (**a**) full model, (**b**) final model, and (**c**) environmental model. The year 1995 is missing from the model results because at least 1 year of Valley Fever incidence data is required to start predicting future values.

DISCUSSION

At this point, our work suggests that fluctuations in incidence are probably due more to human activities (such as construction on previously undeveloped land) or biological processes taking place in the field (see complex systems discussion below), rather than to climatic fluctuations. In contrast with the results reported in Ref. 14, we found[16] only a weak correlation between anomalies in weather variables and incidence in Kern County. The discrepancy might have been due to the fact that climate exhibits important differences in Pima and Kern counties. The mathematical treatments were also different. The differences in the two approaches are mainly in the processing of raw incidence and weather data, although both papers analyzed correlations in a linear model.

Studies to date have demonstrated a strong incidence–climate connection in Arizona,[15] but not in California.[17] Perhaps this is because the latter studies use wind and not PM_{10} as a proxy for spore abundance in the atmosphere. Unfortunately, there are no actual measurements of *Coccidioides* spore concentrations in the atmosphere as a function of PM_{10} concentrations, wind speed, or any other parameter. In the end, we can do no better than give plausibility arguments as to why a particular parameter should be a good proxy without any

hard data to support our surmise. However, given the explanatory power of precipitation and PM_{10} for coccidioidomycosis incidence in Arizona,[15] these predictors should be fully evaluated in Kern County. PM_{10} may be a better proxy for spore abundance in the atmosphere than wind speed, although this may be more so in Arizona than in Kern County, which has one of the worst air pollution problems in the country. Kern County gets large PM_{10} contributions from paved and unpaved road dust, as well as from farming operations (dust that presumably does not contribute spores since the fungus does not grow in cultivated soils). Indeed, as much as 81% of PM_{10} levels is estimated to be of anthropogenic origin in the summer, and 89% in the winter.[20] Kern County is located at the southern end of California's Central Valley and the prevailing winds are northerly, which tends to accumulate pollutants from throughout the valley up against the southern mountains. In Kern County, PM_{10} levels can thus be expected to have a significant contribution from sources not directly related to *C. immitis*. Nevertheless, PM_{10} might be a better proxy to the extent that one is only trying to index dusty days. In phenomenological approaches, such as those in Refs. 13–17, it does not matter what the actual connection is between PM_{10} and spore abundance. It only matters that a good incidence predictor be found.

Interestingly, according to preliminary studies conducted in Arizona,[21] there seems to be a link between smoking and risk of coccidioidomycosis infection: apparently, smokers have a higher risk of infection than nonsmokers; however, smoking cessation restores the risk back to the level of nonsmokers. Clearly, one has to wonder whether this smoking–coccidioidomycosis link results from a suppression of the immune system. And if so, is there a similar effect due to other environmental contaminants (such as NO_x, ozone, and PM_{10})? The effect reported in Ref. 15 might be one instance of a more general effect—perhaps PM_{10} concentrations point to coccidioidomycosis infection not necessarily (or not only) because PM_{10} is a good proxy for *Coccidioides* concentrations in the atmosphere, but because PM_{10} pollution might adversely affect the immune system, thus increasing the risk of infection. Indeed, there is one study[22] in which repeated exposure to diesel exhaust particles showed a sustained pattern of downregulation of T cell–mediated immune responses. This suppression in cell-mediated immunity could be considered a risk for coccidioidomycosis. Furthermore, as pointed out by Terashita and Capone–Newton,[23] PM_{10} is possibly also a marker for other air pollutants. Van Loveren *et al*.[24] found that ozone can inhibit resistance to an intrathecal challenge with *Listeria* monocytogenes, indicating suppression of Th1 immune responses. Again, there may be a similar effect with Valley Fever, turning PM_{10} into a good incidence predictor even if it arises largely from anthropogenic sources, which are unrelated to *Coccidioides* spore concentrations in the atmosphere.

Disentangling the differences between our results and those in Arizona is one of our main endeavors now. Indeed, to that end, we are presently (i) analyzing Arizona data using our GARMA method, and (ii) including PM_{10}

measurements in our Kern County GARMA model. One must keep in mind that comparisons between California and Arizona results are less straightforward than might be realized initially. Not only (i) is *C. immitis* endemic in California, whereas *C. posadasii* is endemic in Arizona, but also (ii) climate is different and it is possible that climatic variations are too small in Kern County to explain incidence anomalies, but not so in Arizona (i.e., there is no compelling reason why an incidence–weather connection should be the same in all endemic areas since *Coccidioides* may react differently to different environments); (iii) the extent to which PM_{10} mirrors spore abundance in the atmosphere is probably different in Pima and Kern counties, owing to the high pollution levels in the latter location; and (iv) generally, different types of soils in the various endemic areas and the extent to which they absorb precipitation may also play a role[21]—for example, if rain goes mostly into run-off, then presumably its effect on fungal growth should be less. These effects, individually and in their interplay, need to be examined in detail to sort out the differences alluded to.

Our GARMA model may lead to different conclusions when PM_{10} concentrations in Kern County are used as additional input parameters. This is because the method relies on a multidimensional minimization search. Therefore, it would not be surprising (at least from a modeling perspective) if this algorithm leads, for example, to both precipitation and PM_{10} being important, even though precipitation did not come up in our original search (when PM_{10} was not considered).

The *Coccidioides*–environment system is interesting not only because of its obvious practical implications-–economic costs[25] and human suffering,[1] but from a theoretical standpoint as well. It seems very likely that the input–response relationships are nonlinear (with the input being the environmental parameters and incidence time series, and the output being the incidence time series); since incidence depends strongly on its own history, there must be feedback loops, and the system clearly has memory; the system boundaries are difficult to determine; it is an open system far from any sort of equilibrium. In other words, the *Coccidioides*–environment system has many characteristics of what is generally known as a complex system: it might be exhibiting an emergent global behavior (large *Coccidioides* population booms) not imposed by a central controller (climatic fluctuations), but resulting from the interactions between the agents (*Coccidioides* and other organisms in its environment).[26] Perhaps methods and techniques developed for totally unrelated complex systems might prove useful in understanding the behavior of Valley Fever time series, especially surges and epidemics.

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