

Statistical modeling of valley fever data in Kern County, California

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Abstract Coccidioidomycosis (valley fever) is a fungal infection found in the southwestern US, northern Mexico, and some places in Central and South America. The fungus that causes it (*Coccidioides immitis*) is normally soil-dwelling but, if disturbed, becomes air-borne and infects the host when its spores are inhaled. It is thus natural to surmise that weather conditions that foster the growth and dispersal of the fungus must have an effect on the number of cases in the endemic areas. We present here an attempt at the modeling of valley fever incidence in Kern County, California, by the implementation of a generalized autoregressive moving average (GARMA) model. We show that the number of valley fever cases can be predicted mainly by considering only the previous history of incidence rates in the county. The inclusion of weather-related time sequences improves the model only to a relatively minor extent. This suggests that fluctuations of incidence rates (about a seasonally varying background value) are related to biological and/or anthropogenic reasons, and not so much to weather anomalies.

Keywords GARMA modeling · Time-series analysis · Valley fever prediction · Coccidioidomycosis · *Coccidioides immitis*

Introduction

Much is known about the biological, medical, and indeed the epidemiologic aspects of *Coccidioides immitis*, the fungus which causes valley fever (coccidioidomycosis) (see Pappagianis (1988), and references therein). *C. immitis* has a complete life cycle as a soil-dwelling organism, but if it is disturbed and becomes air-borne, it is able to infect a host via the respiratory tract when it inhales the fungus spores. About 60% of infected patients report no symptoms (Lee 1944); about 25% exhibit severe flu-like symptoms such as cough, sputum, fever, and muscle aches; the remaining 15% become very ill with pneumonia-like symptoms (e.g. pleurisy and heavier sputum) requiring medication and bed rest. In a small number of these cases (about 0.5–1%), the disease disseminates beyond the lungs to for example the skin, bones, and/or meninges, and it can be fatal. Certain sectors of the population seem to be more susceptible to infection, such as the very young, persons newly arrived to the endemic areas (since immunity develops with infection), and those with impaired immune systems (Pappagianis 1988).

Given its wide geographic distribution, it is apparent that *Coccidioides immitis* is able to flourish within somewhat varied climatic environments. Endemic areas include 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 (Pappagianis 1994). There

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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 (notably Pima, Pinal, and Maricopa Counties, where many coccidioidomycosis cases are reported) gets late summer southwest monsoon rains.

In Kern County, California, where the present study was conducted, the seasonal climate was described in detail in Zender and Talamantes (2006). The area receives in the neighborhood of 16.50 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/s, with maxima usually less than 15 m/s, and very rarely exceeding 20 m/s. The incidence rate (number of cases per 100,000 population) also has a corresponding yearly cycle, with the number generally increasing towards the late fall (with an incidence of the order of 17 per month per 100,000 population), decreasing in the winter, and reaching a minimum in the spring and summer (with an incidence of the order of 4.7 per month per 100,000 population). It is thus natural to expect that environmental fluctuations might affect the rate at which humans become infected (see e.g., Pappagianis 1988). For example, a wetter-than-normal rainy season should help *C. immitis* bloom; windy spells might facilitate the dispersal of the fungus; hot summers can be anticipated to suppress competing organisms, thus enhancing the survival of *C. immitis* (Kolivras et al. 2001). Indeed, the medical community, and the community of Kern County at large have long held that windy days, in particular dust storms, increase the rate of infection. Such anecdotal evidence is well documented in the literature [see e.g., Smith et al. (1946), Hugenholtz (1957), Maddy (1957), Pappagianis and Einstein (1978), Centers for Disease Control and Prevention (1993, 1994, 1996, and 2003), Kirkland and Fierer (1996), Schneider et al. (1997)]. To our knowledge, however, there have been only two mathematical attempts at quantifying and demonstrating this connection. The first such work was presented by Kolivras and Comrie (2003), who found a significant connection between temperature and precipitation, and incidence in Pima County, Arizona. In contrast, the second work, Zender and Talamantes (2006), found 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, for example, Pima experiences monsoon rains, but Kern does not. 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.

Understanding what gives rise to fluctuations in the number of valley fever infections has obvious practical implications. The 1991–1995 epidemic in Kern County had important economic repercussions (Jinadu 1995), as well as human suffering. This is presumably also true of the 2001–present surge in valley fever incidence in Kern County (Larwood and Emery 2005). According to Jinadu (1995), the cost associated with coccidioidomycosis in Kern County in the period 1991–1994 was of the order of \$66.6 million, with hospitalization requiring 63% of that sum, doctor's visits 18%, lost wages 12% and the rest was spent on drugs.

In this paper, we continue to try to assess the effect of weather on valley fever incidence in Kern County and present a model that might be helpful in predicting outbreaks. We look at 9 years of weekly mean atmospheric conditions and try to ascertain if these records can help us predict the weekly incidence some time later. We do not examine the role of longer-term climate fluctuations; the available incidence record is insufficient for that purpose. We examine weekly incidence data starting in January 1995 and ending in December 2003. During this period, weekly incidence varied from zero to about eight cases per week per 100,000 population. The objectives here are different from Zender and Talamantes (2006); this work looked for linear correlations between incidence and monthly climate fluctuations; here, we strive to find a statistical model which allows a degree of prediction. In section 2, we describe the sources and nature of the data we used for the work presented here. In section 3 we specify some mathematical details of the model used in this paper. In section 4, we present the results obtained from that regression, and in section 5 we discuss the effectiveness of the regression and offer some conclusions.

Data description

We obtained the weekly number of reported cases (Jan 1995–Dec 2003) from the Kern County Department of Public Health. These data were then normalized to 100,000 population, and constitute the time series we refer to as incidence N . We note that since many valley fever cases go unreported, incidence is only an approximation to the actual situation (Pappagianis 1988, 1994; Larwood and Emery 2005). Clearly, one can only estimate the level of under-reporting; an infected person may never be tested, however, according to Emery (2006), the Kern County Health Department Laboratory performs about 95% of all the coccidioidomycosis tests in the county. Reporting then takes place directly through laboratory surveillance as opposed to individual health care providers doing the reporting. Furthermore, the Kern County Health Depart-

ment has been using the same standardized case definition (developed in collaboration with the US Centers for Disease Control and Prevention) through the period of study. Reporting is therefore as reliable and thorough as one might hope. Most importantly, the level of reliability has not changed during the period of interest, the analysis we present in this paper is not sensitive to an overall constant scaling factor and so our conclusions are unaffected by a time-independent level of under-reporting.

Weather data were obtained from the National Climatic Data Center (NCDC). The raw data consisted of a series of hourly measurements of (among other parameters) temperature (T), precipitation (P), and wind speed (U). All the measurements were taken at Meadows Field, the county airport in Bakersfield, California. Thus, these time series too must be considered an approximate proxy to the actual parameters of interest, i.e., we could not possibly account for the many micro-climates that might give rise to enhanced valley fever infections in different parts of the county. Furthermore, direct measurements of *C. immitis* air-borne, or even soil abundance do not exist. Instead, we use the wind speed at Meadows Field, which is removed several steps from the desired data. We admit that the use of these parameters can be the cause of some debate as to the interpretation of our results but these data sets are probably as good as any other one might be able to obtain. We computed weekly average time series of the weather parameters from the original NCDC raw time sequences. Our subsequent analysis only used those weekly averages (this part of our procedure is similar to Zender and Talamantes (2006), except that monthly averages were used there).

Methods

We aim to study the effect of three possible environmental predictors, namely, precipitation P_t , wind speed U_t , and near-surface air temperature T_t on the response variable N_t - the reported incidence of valley fever cases in Kern county (t is the time in weeks). We attempt to build a statistical model (linear or non-linear) to determine two components: (i) the degree or pattern of each predictor's effect on the response, and (ii) the statistical significance of these predictors.

Developing a statistical model in the context of this problem is a rather non-trivial task due to two reasons. First, the valley fever data form a time series. This violates a fundamental assumption in the usually practiced generalized linear modeling in which the data are assumed to be independent. Second, it is quite reasonable to assume that valley fever counts at any given time t follow a Poisson distribution with the intensity rate λ , but this assumption complicates the model even more because the normality assumption does not hold. Nonetheless, both features of the

serial nature of the response variable and the Poisson assumption are typical identifiers of modeling with generalized auto-regressive moving average (GARMA) modeling.

GARMA modeling was introduced by Benjamin et al. (2003), who modeled poliomyelitis cases reported to the US Centers for Disease Control and Prevention for the years 1970 to 1983. To our knowledge, this is the only time that GARMA has been used to model disease incidence data. There, the authors specifically treat the case of Poisson regression under a setting which they refer to as GARMA (p, q) models, short for generalized autoregressive of order p and moving average of order q . The fundamental idea is to be able to apply the widely used class of autoregressive moving average (ARMA) models to non-Gaussian data. The ARMA model assumes that the time series is strictly generated by a Gaussian model. As argued above, in cases such as in modeling the valley fever data, the process of interest consists of counts; hence, the normality assumption does not hold. The Poisson assumption here makes the modeling scheme more complex. Benjamin et al. (2003) demonstrated the statistical theory needed to estimate the parameters of the model using the maximum likelihood estimation (MLE). When applying generalized linear models whose response is counts, one may need to take into account the extra variation that stems from the implication of Poisson distribution at time t . This important issue was presented in a paper by Breslow (1984), which led to the idea of quasi-Poisson likelihood regression modeling of the count time series (Kedem and Fokianos (2002) have written a text that gives a comprehensive review of regression modeling for time series).

In essence, we examine here three different GARMA models. We begin our analysis by regarding N_t (the incidence at time t) as the one response variable. We start by considering a GARMA model whose predictors (or independent, or explanatory variables) consist of the autoregressive terms of various lags (i.e., the history of N) as well as the weather variables (P , T , and U). We also include a set of predictors whose role is to account for the seasonality of the incidence. The collection of predictors consists of the following set of 24 independent variables: the three weather parameters U_t , T_t , and P_t , along with six predictors to account for the periodic nature of the series, namely, $\cos(2\pi t/52)$ and $\sin(2\pi t/52)$ to account for the annual seasonality, $\cos(2\pi t/26)$ and $\sin(2\pi t/26)$ to represent any semi-annual seasonality, and $\cos(2\pi t/13)$ and $\sin(2\pi t/13)$ to cover potential quarter-annual fluctuations. Additionally, we consider 15 autoregressive terms N_{t-k} of lags k equal to 1 to 13, 26, and 52 weeks. We note that at this point, we introduce autoregressive terms N_{t-k} purely for mathematical reasons: our intent is to predict the value of N_t - we thus put into the model any variables we suspect might even remotely help us in this prediction task, while at the same time

keeping the number of such explanatory variables to a minimum to keep computational expense down to a reasonable level. We then estimate the coefficients of the model with the method of MLE (see e.g., Box et al. 1994; Benjamin et al. 2003). We call this the full model.

Clearly, if the full model contains sufficient relevant information, one should be able to predict the time series with such a large pool of predictors. However, pragmatically, it is preferable to work with parsimonious models while with more or less the same prediction capabilities. These reduced models also shed light on the relative importance of the various predictors. This reduction necessitates the application of variable search and selection techniques.

We next refine the full model by searching through the space of all possible sub-models. To implement the search we employ a likelihood-based measurement known as the Akaike Information Criterion or the AIC (Akaike 1974). A better model has a smaller AIC. It should be mentioned that searching for the best model in this context is computationally expensive due to the fact that there exist 2^n sub-models in the presence of n explanatory variables. Eventually, we find an optimal model whose AIC is as small as possible. We name this the final model. We should point out that the minimization procedure is a standard way of evaluating a statistical model. Our modeling approach is quite general; however, model parameters and their significance will change as one attempts to model a different time segment of the incidence time series. We would certainly expect those parameters to be different if we considered different data sets.

With the aid of graphical presentation and the calculation of the sum of squares of errors or SSE, we show that the final model may be used to predict the nuances in the incidence

time series. We prefer the use of our final model due to its parsimony, its easier interpretation, and most importantly, the statistical significance of its parameters. Finally, to evaluate the sole effect of the weather-related variables we implement a model with only these effects while excluding the autoregressive terms. We show that this model falls short in predicting the stochastic shocks to the incidence time series. We term this the environmental model.

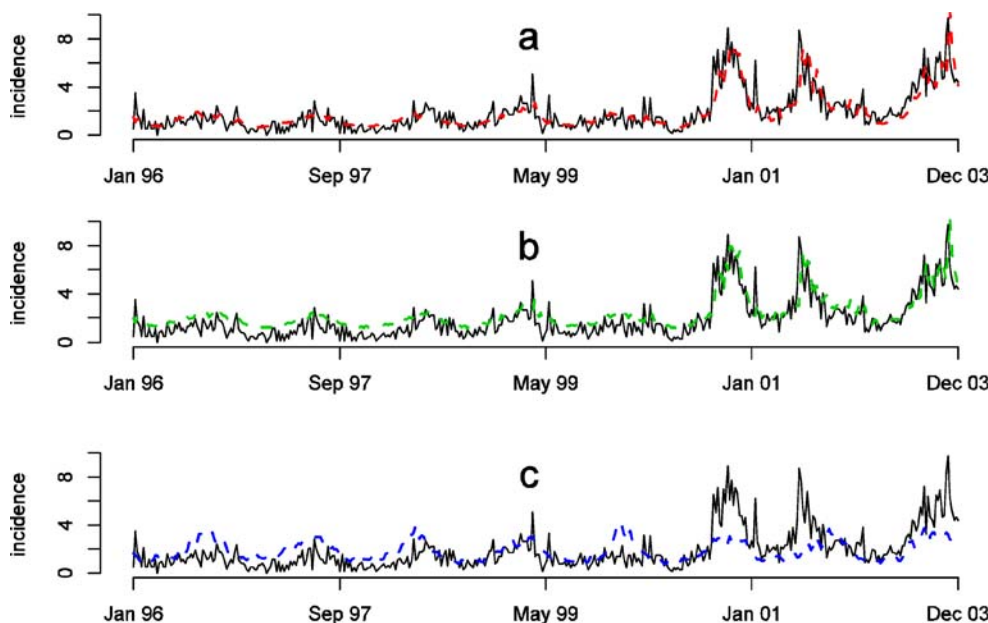
Results

Our AIC-based stepwise search algorithm yields the following estimated model, which we refer to as the final model:

$$\ln \lambda_t = 0.21 - 0.23 \sin(2\pi t/52) + 0.12N_{t-1} + 0.07N_{t-2} + 0.05N_{t-4} + 0.06N_{t-26},$$

in which λ_t represents the rate of the Poisson function of incidences, and the natural logarithm is the link function of the generalized linear model. We note that 0.21 is the constant that corresponds to the background incidence, and the sinusoidal term with the periodicity of 52 weeks confirms the significance of the annual seasonality of the time series. The most important finding here is the absence of weather effects in the final model. The AIC for the final model is 1324, with a residual deviance of 419.8, which follows a chi-squared distribution with 409 degrees of freedom. One may take this as a confirmation for the goodness of fit since the residual deviance and the degrees of freedom are close (Venables and Ripley 1997). In Fig. 1, the top and middle panels demonstrate the predicted time

Fig. 1 Reported valley fever incidence in Kern County, California (cases per 100,000 population) and three models for the period Jan 1996 to Dec 2003. In all three panels, solid lines indicate incidence, and dashed lines correspond to model results: **a** full model, **b** final model, and **c** environmental model. The year 1995 is missing because our model requires at least one year of valley fever incidence to start predicting future values



series resulting from the full and the final models, respectively. In each panel, the prediction time series is overlaid on the incidence data. The SSE for the full model is 368, and 466 for the final model. The statistical significance for the terms included in the final model is shown in Table 1.

The inclusion of N_{t-k} terms but not P_{t-k} , U_{t-k} and T_{t-k} in our full model clearly puts incidence history on a different footing a priori. To ascertain the effect of the asymmetry between incidence and weather histories, we therefore performed two additional and separate analyses: (i) we included P_{t-k} , U_{t-k} and T_{t-k} terms in our full model with lags, $k = 1, \dots, 13$ weeks, and (ii) we included those weather variables with lags $k = 1, \dots, 26$ as well as terms P_{t-k} with $k = 30, \dots, 34$ (which was suggested by the weak correlation between incidence and precipitation 8 months prior found in Zender and Talamantes 2006). We found that the inclusion (in the initial choice of full model) of historical terms associated with weather effects (i.e., P_{t-k} , U_{t-k} and T_{t-k}) does not affect our final model (after our AIC-based minimization search). An important feature of the AIC-based model selection is that most often, the terms included in the final model are statistically significant (but there is no guarantee that this is the case). As a matter of fact, we observed this to be true in our application. This outcome is reassuring, since it resulted automatically from the AIC minimization procedure, as opposed to manually forcing the deletion of any terms. We note, however, that the inclusion of so many parameters in the initial (full) model makes it difficult to interpret the results. This is because we are trying to model a valley fever data set consisting of only $9 \text{ years} \times 52 = 468$ data points. In analysis (i), the number of parameters is $24 + 3 \times 13 = 63$ – of the order of 14% of the number of data points, but in analysis (ii) the number of parameters is $24 + 3 \times 26 + 5 = 107$, which is not much less than the number of data points. Thus, ultimately, our main justification for not explicitly including the histories of precipitation, wind speed and temperature in our full model comes a posteriori: the resulting predictions of the final model are quite close to the observed valley fever incidence data set.

Table 1 The final model. All included terms are statistically significant

Term	Estimate	Std. error	Z-value	P-value
Intercept	0.21	0.066	3.125	0.0017
$\sin(2\pi t/52)$	-0.23	0.060	-3.803	0.0001
N_{t-1}	0.12	0.0025	4.75	2.54e-6
N_{t-2}	0.07	0.027	2.373	0.0176
N_{t-4}	0.05	0.023	1.977	0.0486
N_{t-26}	0.06	0.024	2.540	0.0110

To examine the use of the weather effects in predicting incidence, we ran a model whose predictors consist only of the three weather variables (the environmental model). The last panel in Fig. 1 reveals the weakness of the three variables of speed, temperature and precipitation in the context of prediction. The SSE equals 943 for this model.

Discussion and conclusions

We have presented a model that allows us to predict the incidence N_t of valley fever at some t , given the incidence history for earlier times. In section 3, we presented various models which include different amounts of input data. When the time series corresponding to N , U , T , and P are all accounted for, the fit to the observed incidence of valley fever is very good as measured by the SSE. When only the previous incidence history is included in the model, however, the SSE does not increase by much. When we include only the U , T , and P histories in the model, the predicted incidence values are significantly worse, again, as measured by the SSE. Our main conclusion is therefore that the dependence of incidence rate fluctuations on weather parameters in Kern County is rather weak. Evidently, Kern has the right environment for *C. immitis* to thrive, but given that the fungus is well established, and that this causes a certain seasonally dependent incidence background, the *fluctuations* about that background tend to exhibit only a weak dependence on weather events. This result is entirely consistent with those of Zender and Talamantes (2006), where only a weak linear (lag) correlation between monthly mean climate and valley fever incidence was found. We surmise that the reasons behind the observed fluctuations in valley fever incidence in Kern County (vis á vis the 1991–1995 epidemic, and the 2001–present surge) are biological and/or anthropogenic in nature - most likely new construction on previously undisturbed soil. We suggest that weather fluctuations, at least on the weekly scale investigated in this work and the monthly scale used in Zender and Talamantes (2006), are too small to explain fluctuations in incidence. This is especially clear with temperature; it is most likely also true for precipitation, which exhibits the largest fluctuations of the weather variables investigated.

Our model allows for the prediction of the value of the incidence N_t at time t given certain required values N_{t-k} . This is a prediction in the following sense. Given the *measured* values of N_{t-k} , the model “returns” a prediction N_t . Prediction values are obtained by plugging in the maximum likelihood estimations of the coefficients into our final model. We note that attempting to use this model to *forecast* values N_t (where t is in the future) would be unwise because one would need to rely on values N_{t-k} which themselves were predictions (not *measurements*).

The uncertainty in such forecasted values of N_t would thus grow very rapidly.

It is undeniable that the available data are not of optimal quality; we use weather observations at the county airport and take them as representative of the whole county; the reported incidence numbers are most likely less than actual infection rates (Pappagianis 1988; Larwood and Emery 2005); we use precipitation and wind speed as proxy for *C. immitis* abundance in the soil and the atmosphere; it takes some variable number of weeks (perhaps five to six) between infection and reporting (Larwood 2003). These problems add to the difficulty in interpreting our results; nevertheless, it is quite surprising and reassuring that the modeling results come out so close to the observations. This is probably due to the strong dependence of incidence on its own history, and so modeling the problem is (fortuitously) only weakly dependent on the details of the fluctuations of the environmental data. The fact that our model so closely resembles reported incidence data is an indication that our approach in minimizing the model error has been successful.

At this point, the most likely and feasible direction our work might take is to investigate the universality of our results. That is, it would be interesting to see whether modeling incidence data in other areas of the southern San Joaquin Valley might give qualitatively similar results to Kern County. Perhaps more interestingly, we would want to see if endemic areas with different climates (such as Pima, Pinal and Maricopa counties in Arizona) can be modeled similarly to the results in this work, or if weather and climate anomalies explain more incidence there than in Kern County. Furthermore, we might try to examine the effect of using a different proxy for spore abundance in the atmosphere; for example, we might use PM₁₀ measurements (however, one must be mindful of the fact that these numbers may be increased due to factors completely unrelated to *C. immitis* spores, e.g., industrial processes and increased vehicular traffic). We would like to emphasize that our findings are only interpretable within the framework of the variables that we originally included in our full model. In other words, this modeling scheme should be viewed considering that in a study of this nature there exists a number of other potentially interesting variables that may affect valley fever incidence in Kern County. The inclusion of such auxiliary sets of variables may change the overall profile of our final model as presented in this paper.

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