2.2 DOES CLIMATE CONTROL VALLEY FEVER INCIDENCE IN CALIFORNIA?

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1. INTRODUCTION

Coccidioidomycosis is a systemic infection caused by inhalation of airborne spores of *Coccidioides immitis*, a soil-dwelling fungus found in the southwestern United States, parts of Mexico (*Maddy and Coccozza*, 1964), and Central and South America (*Centers for Disease Control and Prevention*, 1994). *C. immitis* thrives in moist soils, is spread by wind events, and therefore has many environmental risk factors. Epidemiologic studies in the 1930's (*Deresinski*, 1980; *Larwood*, 2000) linked coccidioidomycosis to the regional disease known as San Joaquin Fever, also known as valley fever. Risk management and cost-effectiveness studies show that a vaccine for valley fever is plausible and should be administered to newborns in highly endemic counties including Kern in California and Pima in Arizona (*Galgiani*, 1999; *Barnato et al.*, 2001). These and earlier studies (*Centers for Disease Control and Prevention*, 1994, 1996) recommend intensifying efforts to better characterize climate risk factors for acquiring infection. This study explores climate-related risk factors for valley fever in Kern County and quantifies their level of significance.

Early studies of environmental causes of valley fever (*Smith et al.*, 1946; *Maddy*, 1957; *Hugenholtz*, 1957) elucidated a lifecycle that accounts for many observed features of *C. immitis* blooms and subsequent coccidioidomycosis incidence. *Pappagianis* (1988) synthesized the climatological aspects of this lifecycle gathered from those and following studies. *C. immitis* thrives in the soil ("blooms") during wet periods lasting several weeks. Infections tend to occur in the dry season when soils are most mobile. Incidence often increases after a heavy wet season following a prolonged dry spell.

In the most quantitative analysis of climate controls on valley fever incidence to date, *Kolivras and Comrie* (2003) found that antecedent precipitation and temperature are moderate climate risk factors for valley fever in Pima County (which includes Tucson), Arizona, USA. They developed a multivariate model to predict valley fever incidence in Arizona in a given month based on climate conditions and anomalies in the antecedent 3.5 yr. Moreover, *Kolivras and Comrie*'s statistical model uses and predicts a metric called the transformed incidence anomaly. This is the monthly incidence anomaly relative to the annual (rather than climatological, or climatological monthly) mean. The maximum transformed incidence anomalies they reported in Pima County are about 10%, and their statistical model predicts up to half of some anomalies.

The transformed incidence is insensitive to uniform increases in monthly incidence which result in an absolute annual increase (e.g., an epidemic) but which do not change the relative contribution of each month to the annual incidence. By contrast, the 1991–1995 epidemic in Kern County increased interannual and intra-annual variations in incidence by about 1000% (ten-fold). This appears to be the largest well-documented valley fever epidemic on record.

Previous studies identify no clear cause for the 1991–1995 epidemic (*Centers for Disease Control and Prevention*, 1994; *Jinadu*, 1995; *Kirkland and Fierer*, 1996). The most likely climate factor contributing to the epidemic was the increased rainfall that ended a five year drought in California in March, 1991 (*Jinadu*, 1995; *Kirkland and Fierer*, 1996). The following two winters were twice as wet as normal (*Jinadu*, 1995). Possible exacerbating demographic factors were an increased immunosuppressed population, and less prior exposure (which develops immunity) in the general population (*Kirkland and Fierer*, 1996; *Centers for Disease Control and Prevention*, 1996).

We analyze the links between climate and *C. immitis* epidemiology using the Jan. 1980 to Dec. 2002 record (23 years) of monthly statistics from Kern County, California. Our objectives are twofold: First, we explore climate-related risk factors for valley fever in Kern County and quantify their level of significance. In the second portion of our study we contrast our results from Kern County to results from a similar study in Pima County, Arizona (*Kolivras and Comrie*, 2003) which experiences a significantly different climate. This comparison shows us the extent to which valley fever predictability depends on local climate, and how that may differ with climate regime.

2. DESIGN

2.1 *Monthly Regression Analyses*

Climate variables in Kern County are from the Solar and Meteorological Surface Observational Network Dataset (SAMSON, available from National Climatic Data Center, Asheville, North Carolina) for 1961–1990. We use NOAA Hourly United States Weather Observations (HUSWO) for 1990–1995, NOAA Integrated Surface Hourly Observations (ISHO) for 1995–2000, and NWS Hanford Forecast station website for daily data in 2001–2002. All four datasets come from measurements taken at Bakersfield airport. Hourly and daily weather data are averaged to obtain monthly means.

Valley fever incidence statistics for Kern County were obtained from the California Department of Health Ser-

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vices (CDHS). Monthly incidence reports are available from 1980–2002, while annual incidence data pre-date 1980. Kern County is the national center for serologic testing for valley fever. The high awareness in Kern County leads to better reporting.

We base our analysis on the climatological monthly anomalies of incidence and climate data. The very strong annual cycles of the (raw) time series we considered dominate the physical picture—correlation analysis of these time series only shows this effect, and nothing else. We therefore removed the annual cycle from all data. The resulting time series are strongly autocorrelated (e.g., a particularly warm July likely follows an unusually hot June). Analysis based on *these* time series results in artificially strong correlations between incidence and meteorological parameters, while teaching us nothing about incidence anomalies in general, and epidemics in particular. We therefore removed those autocorrelations by applying an autoregression procedure of sufficiently high order (*Chatfield*, 2004). Finally, we performed lag correlation analyses only after correcting for annual cycles and time-series autocorrelations.

2.2 *Epidemiology*

We are most interested in identifying climate and soil-related anomalies in *C. immitis* in order to assess the susceptibility of endemic regions to increased incidence of valley fever given accurate predictions of seasonal-to-interannual climate anomalies. Seasonal-to-interannual climate predictability has improved in recent years as teleconnections between climate modes (e.g., ENSO) and regional climate become better understood and represented in models (e.g., *Glantz et al.*, 1991). Unfortunately, data abundance of *C. immitis* in soil are unavailable. At this time the best proxy available is case incidence, even though many steps separate growth of *C. immitis* in soil from case incidence (*Kolivras and Comrie*, 2003).

The absolute incidence $N_0\,[\#\,\mathrm{yr}^{-1}]$ of valley fever in Kern County from 1960–2002 and the incidence per unit population $N\,[\#\,\mathrm{yr}^{-1}\,(100{,}000)^{-1}]$ are nearly identical in shape (Figure 1). We always use N rather than N_0 for statistical comparisons. During this period the Latino population fraction increased about 7% per decade since 1970 to about 35% now. This demographic trend is not detectable in the incidence statistics, suggesting that Latinos are as susceptible as the original demographic.

The inter-annual variability (one standard deviation) in annual valley fever incidence from 1960–2002 is $102\,\mathrm{yr}^{-1}\,(100{,}000)^{-1}$, 120% of the mean incidence of $85\,\mathrm{yr}^{-1}\,(100{,}000)^{-1}$. The interannual variability from 1991–2002 is $164\,\mathrm{yr}^{-1}\,(100{,}000)^{-1}$, significantly greater than $23\,\mathrm{yr}^{-1}\,(100{,}000)^{-1}$ for the period 1960–1990. Incidence N in 2001 and 2002 was higher than any previously recorded level except the epidemic of 1991–1995 (*Jinadu*, 1995).

The intra-annual variability is shown for 1980–2002, when monthly incidence data were available. The fractional intra-annual variability $\bar{\sigma}$ is the standard deviation

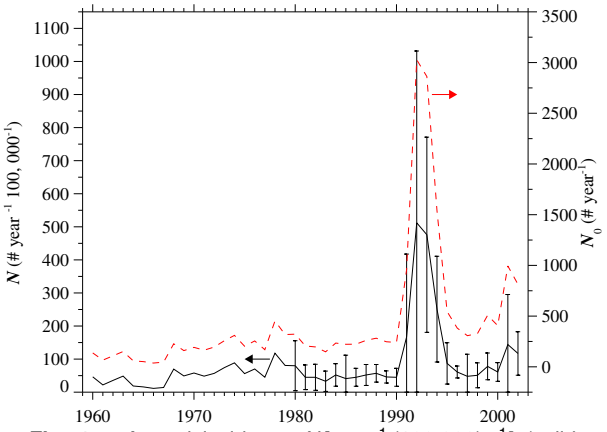

Fig. 1: Annual incidence $N\,[\#\,\mathrm{yr}^{-1}\,(100{,}000)^{-1}]$ (solid line) and total number of reported cases $N_0\,[\#\,\mathrm{yr}^{-1}]$ (dashed line) of valley fever in Kern County from 1960–2002. Bars show two standard deviations of each year's monthly incidence statistics projected to annual rates.

of annual incidence rates computed from monthly rates multiplied by twelve. Despite large interannual changes in N, the mean $\bar{\sigma}$ is close to $122\,\mathrm{yr}^{-1}\,(100{,}000)^{-1}$. Thus the monthly incidence is within $244\,\mathrm{yr}^{-1}\,(100{,}000)^{-1}$ of the annual mean incidence in 10–11 months in most years.

2.3 *Climatology*

Coccidioidomycosis incidence $\bar{N}\,[\#\,\mathrm{mo}^{-1}\,(100{,}000)^{-1}]$ in Kern County and the climate risk factors that may be associated with it show pronounced annual cycles (Figure 2). Monthly valley fever incidence since 1980 shows a strong annual cycle superimposed on a relatively uniform background rate of order $5\,\mathrm{mo}^{-1}\,(100{,}000)^{-1}$. Exposures due to non-environmental causes, e.g., construction, excavations, are expected to contribute to the background incidence (*Maddy*, 1957; *Kolivras et al.*, 2001). Incidence increases from $4.7\,\mathrm{mo}^{-1}\,(100{,}000)^{-1}$ during spring months (Apr–Jun) to $17\,\mathrm{mo}^{-1}\,(100{,}000)^{-1}$ during fall (Oct.–Dec.), when 60% of all cases are reported. One should keep in mind that the minimum time from exposure to incidence is about two weeks, and that many cases progress unreported for months, until victims' conditions are serious enough to require medical care (*Pappagianis and Einstein*, 1978). On average, it takes about five weeks from infection to reporting (T. R. Larwood, personal communication, 2003).

The most variable climate characteristic in Kern County is rainfall. The climatological mean precipitation $\bar{P}$ from 1961–2002 is $15.8 \pm 23.1\,\mathrm{cm\,yr}^{-1}$. *C. immitis* prevalence decreases in climates with precipitation rates $\bar{P} < 10\,\mathrm{cm\,yr}^{-1}$ and $\bar{P} > 50\,\mathrm{cm\,yr}^{-1}$ (*Kolivras et al.*, 2001). Thus Kern County receives enough precipitation for growth of *C. immitis* in average and moist years. Incidence in California peaks from Oct.–Jan., the end of the dry season, as noted in previous studies (e.g., *Smith et al.*, 1946; *Pappagianis*, 1988). Precipitation from the cold northwesterly frontal systems peaks in late winter, and seems to reduce further incidence, perhaps by

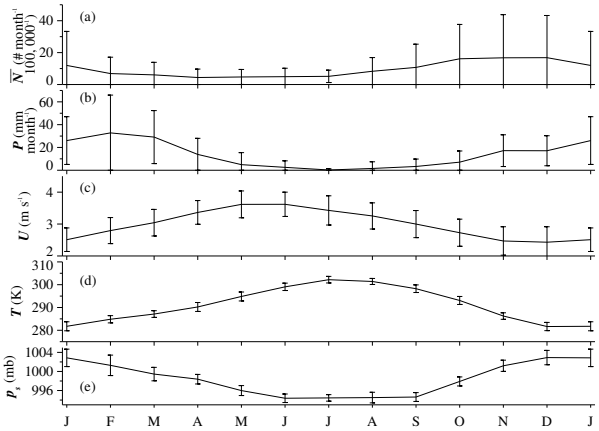

Fig. 2: Annual cycle of coccidioidomycosis incidence and potential climate risk factors from 1980–2002. Shown are monthly mean (a) incidence $\bar{N}$ [# mo^{-1} (100,000)$^{-1}$] (b) precipitation $\bar{P}$ [mm mo^{-1}], (c) wind speed $\bar{U}$ [m s^{-1}], (d) surface temperature $\bar{T}_s$ [K], (e) surface pressure $\bar{p}_s$ [mb]. Bars span two standard deviations of the inter-annual variability computed separately for each month. Standard deviations computed using 1980–2002 data for incidence, 1961–2002 for climate variables.

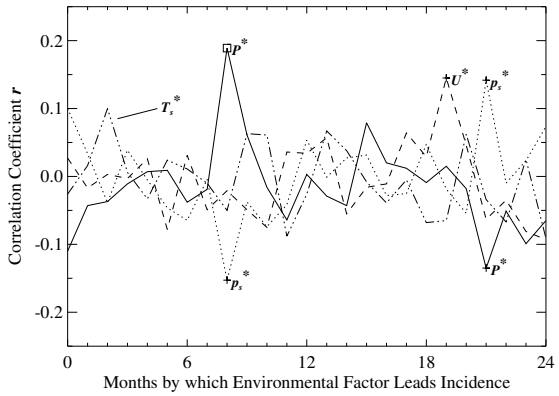

Fig. 3: Lag correlation coefficient r between climatological monthly valley fever anomaly N^* and climatological monthly anomalies of four potential climate risk factors: precipitation P^*, wind speed U^*, surface temperature T_s^*, and surface pressure p_s^*. Plusses (+) and squares (□) indicate confidence statistics p better than 5% and 1%, respectively.

dampening soil and suppressing Aeolian erosion.

The climatological mean wind speed $\bar{U}$ in Kern County from 1961–2002 is 3.0 ± 0.6 m s^{-1}. Instantaneous wind speed U (not shown) from Kern County exceeds the 6–15 m s^{-1} at 10 m height required for soil deflation many times each month. Seasonal winds peak in May–July, the beginning of the dry season. The seasonal coincidence of peak winds with drying soil in Kern County seems to favor Aeolian distribution of arthroconidia, and thus infection, in summer.

3. RESULTS

3.1 *Monthly Climatology*

Similar to previous studies in other regions (*Hugenholtz*, 1957; *Kolivras and Comrie*, 2003), we examined correlations between annual cycles of valley fever incidence, precipitation, winds, and temperature (cf. Figure 2). Figure 3 shows the unranked (Pearson) linear correlation coefficient r between the autoregression-corrected climatological monthly valley fever anomaly N^* and the (autoregression-corrected) climatological monthly anomalies of four potential climate risk factors: precipitation P^*, wind speed U^*, surface temperature T_s^*, and surface pressure p_s^*. The results are qualitatively similar if ranked (Spearman) correlations r_s are used instead.

The confidence statistic p is only better than 1% once, for correlation between precipitation anomaly eight months antecedent. The confidence statistic p is better than 5% once for wind speed anomaly (19 months antecedent), once more for precipitation anomaly (21 months antecedent), twice for surface pressure anomaly (discussed below), and never for surface temperature anomaly. Table 1 summarizes these results. It shows, in decreasing order of significance, all statistically significant confidence statistics $p < 0.05$ between valley fever anomalies and climate anomalies in Figure 3. All associated lag-correlation coefficients r and r_s are < 0.20. Hence our central result is that climate anomalies do not provide a robust method for predicting incidence in Kern County, based on 23 years of monthly data.

3.2 *Epidemic Years*

During the 1991–1995 epidemic, annual incidence N increased five-to-tenfold, from 50 to 500 yr^{-1} (100,000)$^{-1}$ (cf. Figure 1). In non-epidemic years, 65% of cases are reported between November and January. The epidemic amplified this strong late-fall early-winter seasonality. During the 1991–1995 epidemic, 59% of the anomalous (actual minus expected) cases were reported in Nov.–Jan. This dramatic seasonal increase appears in the annualized monthly variability in N (Figure 1). Incidence reports for 2001–2002 also show a significant increase above the long term background level. Thus understanding factors contributing to epidemic outbreaks is of current concern in California.

In order to help distinguish climatic from demographic causes of the 1991–1995 epidemic, we divide the data into pre-epidemic, epidemic, and post-epidemic time-series and analyze them separately. Table 2 describes the six subset time periods that we extract and analyze separately from the full time-series. We examine these subset time-series for significant changes in the correlations between precipitation and wind speed anomalies with valley fever incidence.

Figure 4 shows the linear correlation coefficient r between the monthly valley fever incidence anomaly N^* and the precipitation anomaly P^* for the seven different periods enumerated in Table 2. (Series A, containing all available monthly data, also appears in Figure 3). The trends and phasing generally agree among the subset

Table 1: Significant Correlations with Climate Anomalies[a]

Anomaly	# mo.[b]	r[c]	r_s[d]	p[e]
Precipitation P^*	8	0.19	0.11	0.0020
Precipitation P^*	21	−0.14	−0.13	0.028
Wind Speed U^*	19	0.15	0.074	0.018
Sfc. Pressure p_s^*	8	−0.15	−0.08	0.018
Sfc. Pressure p_s^*	21	0.14	0.16	0.028

[a]Sample size $M = 264$ for P^*, U^*, and T_s^*; $M = 240$ for p_s^*.

[b]Number of months by which monthly climate anomaly x^* leads monthly valley fever anomaly N^* for this correlation

[c]Pearson correlation coefficient

[d]Ranked (Spearman) correlation coefficient

[e]Confidence statistic (probability that incidence and climate factor are uncorrelated)

time-series. The highly significant correlation ($p < 0.01$) of wet anomalies with incidence anomalies eight months later appears in the entire 23 yr record (Series A) and from 1980–1995 (Series C). Examination of monthly time-series (not shown) reveals that winter (February–March) rains influence incidence the following winter (December–January), a pattern noted previously (*Smith et al.*, 1946; *Hugenholtz*, 1957; *Pappagianis*, 1988; *Jinadu*, 1995; *Kolivras and Comrie*, 2003).

Since the epidemic, from 1996–2002 (Series E), precipitation anomalies occur 11 mos before incidence anomalies with $r = 0.30$ ($p = 0.0059$). Incidence during the 1991–1995 epidemic (Series F) shows no highly significant features. We note that the correlation required for a given confidence level is much greater for Series F due to its short length (60 months). The significant negative correlation with precipitation 11 mos prior may be a false positive since this would be inconsistent with Series E and with what is known presently of the lifecycle of coccidioidomycosis. On the other hand, *Zender and Kwon* (2005) show that dry anomalies in the previous rainy season are highly significantly associated with increased soil dispersion nine months later in many of Earth's dustiest regions. Hence increased incidence two months following increased dispersal is a plausible alternative explanation of the Series F behavior. Considered altogether, the indications of a significant connection between rainfall and incidence changes in epidemic years are unclear and somewhat contradictory.

Figure 5 shows the linear correlation coefficient r between the valley fever incidence anomaly N^* and the wind speed anomaly U^* for periods in Table 2. Most of the statistically significant relationships of wind speed to incidence anomalies occur since the epidemic, from 1996–2002 (Series E). During this period, wind speed anomalies occur 5 mos before incidence anomalies with a correlation $r = 0.32$ ($p < 0.01$). However, the significant correlations rapidly alternate from positive to negative during the first six months before incidence. Thus interpreting the significant wind speed anomalies as causally related to valley fever is problematic. Since 1991 (Series G) incidence anomalies occur eight months after opposite wind speed anomalies with $r = 0.42$ ($p < 0.01$). This feature may be a cross-correlation artifact. As discussed above, winter rainfall anomalies dominate incidence anomalies with an eight month lag from 1980–2002 (Figure 4). Winds are slowest in winter (Figure 2c) and so may (coincidentally) anti-correlate with 1991–2002 monthly incidence anomalies, but not with the entire incidence dataset (Series A).

Table 2: Time Series Analyzed Separately

	Description	Start	End	# mo.[a]
A	Entire 23 year record	1980	2002	276
B	Until epidemic start	1980	1990	132
C	Until epidemic end	1980	1995	192
D	Epidemic omitted	1980	2002	216
E	Epidemic end to record end	1996	2002	84
F	Epidemic only	1991	1995	60
G	Epidemic start to record end	1991	2002	144

[a]Number of months in period

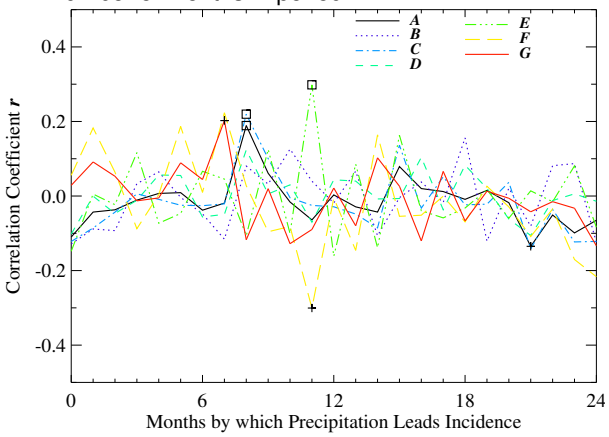

Fig. 4: Lag correlation coefficient r between valley fever incidence anomaly and precipitation anomaly P^* for periods in Table 2. Plusses (+) and squares (□) indicate confidence statistics p better than 5% and 1%, respectively.

3.3 *GARMA Analyses of Weekly Incidence*

The standard correlation techniques described in Section 2.1 are useful to identify correlations in anomalies of incidence and climate. The Generalized Auto Regressive Moving Average (GARMA) technique (*Benjamin et al.*, 2003) can test more sophisticated hypotheses with fewer assumptions. We use the GARMA technique to analyze the *weekly* incidence and weekly weather records from 1995–2003 (*Talamantes et al.*, 2006).

Three GARMA models are constructed:. The first

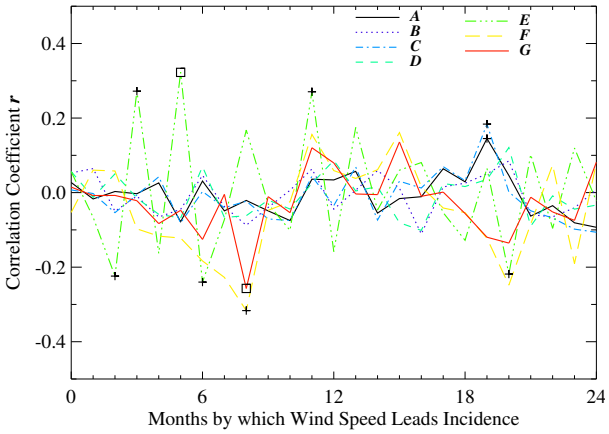

Fig. 5: As in Figure 4, but for lag correlation coefficient r between valley fever incidence anomaly and wind speed anomaly U^*.

uses previous weather and incidence data to predict subsequent incidence. The second uses only previously incidence data to predict subsequent incidence. The third uses only previously weather data to predict subsequent incidence. Differences in skill between the first and second models indicate the the power of previous weather to explain subsequent incidence.

3.4 *GARMA Results*

Using a sum of squares of errors (SSE) technique to quantify the model performance shows that prior incidence, precipitation, wind speed, and temperature (N, P, U, and T_s) accurately predict subsequent N for the time period 1996–2003 (Figure 6a). This formulation, called the *full model* incorporates 24 pieces of prior and current incidence and current environmetal data to predict subsequent incidence. Inclusion of prior environmental data does not improve accuracy.

SSE shows that the predictive accuracy does not degrade significantly when environmental data are removed from the mix of information used to predict incidence. Moreover, using a technique called Akaike Information Criterion (AIC) search, we reduced the prior incidence data required to four points representing the incidence one, two, four, and twenty-six weeks prior to the prediction (Figure 6b). This result, called the final model is parsimonious because it requires many fewer data than the full model, at little or no cost in predictive skill.

Finally, we tested the efficacy of using only environmental factors to determine subsequent incidence. The result, called the environmental model, lacks predictive skill relative to the incidence-only final model (Figure 6c). Since environmental variables do not significantly improve the full model, and incidence alone suffices to hindcast the eight year weekly record, we find that weekly weather has little or no explanatory power for incidence variations. *Talamantes et al.* (2006) give full details of the procedure and results.

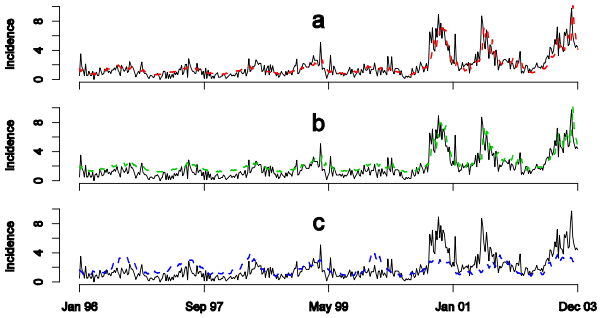

Fig. 6: Reported weekly valley fever incidence (cases per 100,000 population) in Kern County, California (solid lines) for the period Jan. 1996 to Dec. 2003, and three models (colored dashed lines). Models using GARMA technique (a) Full model, (b) final model, and (c) environmental model. 1995 is missing because the model requires at least one year of data to start predicting future values. (*Talamantes et al.*, 2006)

3.5 *Conclusions*

We tested monthly and weekly precipitation, wind speed, and temperature anomalies as potential predictors for valley fever incidence anomalies in Kern County from 1980–2003. The only climate indicator with highly significant correlations with incidence during this period is the precipitation anomaly. Precipitation anomalies eight months antecedent to reporting explain only up to 4% of monthly variability in subsequent valley fever incidence.

The GARMA models allow us to predict valley fever incidence $N(t)$, given the incidence history for earlier times. 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 (the fit is still very good). 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 *Zender and Talamantes* (2006), who found only a weak linear (lag) correlation between monthly-mean climate and valley fever incidence.

We surmise that the reasons behind the interannual fluctuations in valley fever incidence in Kern County (i.e., the 1991–1995 epidemic, and the 2001–present surge) are biological and/or anthropogenic in nature, perhaps soil excavation. Weather and climate fluctuations, at least on the weekly and monthly scales investigated in *Talamantes et al.* (2006) and *Zender and Talamantes* (2006), are too small to explain more than 5% of incidence fluctu-

ations. This is especially clear with temperature; and it is most likely true for precipitation, which exhibits the largest fluctuations of the weather variables investigated.

None of the potential climate indicators of incidence that we tested are highly significantly correlated with the 1991–1995 epidemic. Other potential univariate climate indicators of incidence (e.g., accumulated seven-month precipitation, wind gustiness) and multi-variate climate indicators (e.g., drought index) may show more predictive skill than those we tested (e.g., *Komatsu et al.*, 2003). Seasonal climate predictors of valley fever in Kern County are similar to, but much weaker than those in Arizona, where previous studies find precipitation explains up to 75% of incidence. Causes for the discrepancy between climate associations with valley fever in California and Arizona require further study.

Incidence reports for 2001–2003 in Kern County show a significant increase above the long term background level unprecedented except for the 1991–1995 epidemic. Reliable predictors of incidence will be extremely valuable whether or not current incidence rates continue to rise. Higher resolution temporal and spatial monitoring of soil conditions in Kern County may improve our understanding of climatic antecedents of valley fever epidemics.

ACKNOWLEDGEMENTS

We thank F. Beltran (CSUB), E. Chaput (KCDPH), K. Emery (KCDPH), T. Larwood, R. Reynolds (USGS), S. Sebesta (CDHS), and The Valley Fever Center for Excellence for helpful discussions and data. This research was supported in part by NASA Grants NAG5-10147 and NAG5-10546 and by the NCAR Advanced Studies Program.

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