CLIMATE AND VALLEY FEVER (COCCIDIOIDOMYCOSIS)

By

Korine Nicole Kolivras

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SIGNED: Konne N. Kolivras

APPROVAL BY THESIS DIRECTOR

This thesis has been approved on the date shown below:

Andrew C. Comrie
Associate Professor of Geography
and Regional Development

12/7/00
Date

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ABSTRACT

This thesis provides the results of research that explores the relationship between climatic conditions and the incidence of valley fever in Pima County. Valley fever is caused by a soil-dwelling fungus, *C. immitis*, which responds to changes in climate conditions.

Bivariate and compositing analyses provided the basic relationships necessary for the development of monthly multivariate models. The models are designed to predict deviation from mean incidence based on past, current, and forecast climate conditions.

Temperature and precipitation are important predictors of incidence, and were used in model development. Winter temperature and precipitation variables were included in the model more frequently than variables in other seasons, and most variables were on the time scale of one year or more prior to the month being predicted. Model results were moderate, and months with high incidence can be predicted more accurately than months with low incidence.

Chapter 1 - Introduction

Research in climate and health has gained momentum in recent years. Growing concern over the broad impacts of climate variability and climate change has lead to an increase in research initiatives designed to improve the understanding of those impacts. The body of research on overall effects of climate variability and change includes effects on agriculture, tourism, energy, water resources, and other areas as well as human health (McMichael 1997). To appreciate the ways in which climate change will impact a disease or health problem, a basic understanding of the relationship between climate and the disease is needed. With this understanding, the association between climate variability and disease can be explored. It is within this context that the research presented here is framed. This thesis presents research conducted to understand the relationship between climate variability and valley fever (coccidioidomycosis).

Valley fever was first identified in Argentina in 1892 (Pappagianis 1980). The fungus causing the disease, *Coccidioides immitis* (*C. immitis*) was first recognized within the United States in 1932 in California (Stewart 1932), and has subsequently been linked to variations in climate conditions. The research presented in this study, examining the relationship between valley fever incidence and climate, falls within the climate and health area, drawing from traditions in medical geography and applied climatology.

1.1 Medical Geography

As a sub-discipline, medical geography is broadly based and interdisciplinary, drawing on a wide variety of other fields of study including biology, epidemiology, sociology, parasitology, meteorology, biostatistics, and many others (Meade 1988). Within geography, medical studies often utilize methods in both human and physical geography by recognizing the importance of both areas to the understanding of patterns of disease and health care. Methods applied within the field can be qualitative or quantitative in nature, or a combination of both. Studies employing various statistical techniques are useful for comparing rates of disease in populations and rates of increase, while qualitative methods provide a means for determining individual health care access or disease acquisition through interviews and surveys.

Medical geographers add a "geographic perspective" to work on disease distribution and health care systems, and often collaborate with researchers in related fields. (Meade 1988). Medical geographers contribute beyond the field of geography by adding a spatial perspective to medical research (Meade 1988). Geographers employ methods to examine population and movement relationships, social institutions, and political controls that are related to disease patterns, as well as environmental characteristics associated with disease. With an integrative perspective, geography incorporates traditions and methods that are useful for understanding disease distribution across disciplines.

Research in medical geography falls into two categories: disease ecology and health services research (Gaile 1989). The main goal of research in disease ecology research is to understand the relationship between health and disease in the context of disease etiology, and to promote adaptations by people and/or the environment (Gaile 1989). Disease ecology focuses on explaining patterns of morbidity and mortality, as they relate to social, environmental, and cultural processes. This category of medical geography can be further subdivided into studies of infectious and chronic diseases, as well as infant mortality and malnutrition (Gaile 1989). Alternatively, health services research examines a wide variety of health-related issues including access to health care, equity, and social institutions present in the medical field. Relevant studies in health services research include work by Sara McLafferty that examines health and disease in urban areas, and a recent trend in decreasing quality of life with respect to healthcare in inner cities (McLafferty 1990; McLafferty 1992). The approach in this thesis is empirical and quantitative in nature, and specifically fits into the disease ecology area of medical geography, through the study of an infectious disease.

1.2 Climate and Health

Climate and health research falls within the realm of applied climatology, which seeks to understand the general effects of climate variability and change on various aspects of society. Much of the research in the area of climate and human health focuses on the effects of climate change on disease outbreaks and health problems related to extreme events. The Intergovernmental Panel on Climate Change (IPCC) has included the effects of climate change on human health in its second report (Houghton 1996). It is expected that climate change will impact health both directly and indirectly. Direct effects include increased mortality from heat waves and extreme weather events, while indirect effects include changes in disease incidence resulting from modifications in a vector's breeding habitat as well as modifications to the environment in which non-vector pathogens live.

In spite of recent attention by research agencies and the media, questions surrounding the influence of climate on disease do not reflect a new trend. Twenty years prior to the release of the IPCC's second report on climate change impacts, including the chapter on human health, the World Meteorological Organization addressed the impacts of climate variability on health at the World Climate Conference (Weihe 1979). The interest in the effect of climate on disease extends, however, even farther into the past. Haviland (1855) discusses observations made by Hippocrates approximately 2300 years ago with regard to the climate of a certain region and the type and severity of disease found in the location. It is believed that Hippocrates was the first physician to link disease with climate conditions (Snorrason 1964). Epidemics in the past were analyzed with respect to temperature, wind speed and direction, air pollution, and air pressure, as well as the general season of the year (Haviland 1855). These early studies searched for a link between climate conditions and disease incidence, and are similar to studies being conducted today. Climate conditions have more recently been linked with specific chronic and infectious diseases including diabetes, leukemia, sclerosis, tuberculosis, appendicitis, and mental illness (Mills 1939). Susceptibility of humans to heat and cold is also a frequently mentioned stress, as well as allergens and pollutants (Mills 1939; Burakowski 1964; Dingle 1964). Studies conducted in the past are similar to current research in climate and health, however longer data records and more sophisticated techniques are now available.

Thermal stress is a frequently cited example of a direct impact of climate change. Mortality increases more rapidly with very high temperatures than with extremely low temperatures, and mortality is lowest within a range of moderate temperatures (Houghton 1996). With climate change, it is expected that mortality related to high temperatures will increase as the number of deaths related to cold extremes decrease. However, it is likely that net mortality will increase since more deaths are related to extremely high temperatures (Houghton 1996). The variability of temperatures and the resulting impacts on humans within the United States has been well studied by geographers (Kalkstein et al. 1987; Kalkstein et al. 1996; Smoyer et al., 2000). The majority of research conducted examining thermal stress has concentrated on mortality due to high temperatures in the summer season through the evaluation of heat indices and the development of a warning system (Kalkstein, 1983; Kalkstein, 1996). Other studies have examined winter weather stress (Kalkstein, 1987), however as previously stated, more deaths are related to high temperatures than extreme cold.

Indirect effects of climate variability and change are often felt through the enlarged range and increased activity of a vector. Malaria is discussed frequently in the literature as having strong connections to climate conditions. The disease's vector, the Anopheles mosquito, requires warm, wet conditions, and is found in tropical regions (Epstein 1998). The reliance on moisture to support the mosquito suggests that incidence of malaria fluctuates with climate variability on an annual basis as well as inter-annually (Patz et al. 1998). Also, it is estimated that as the climate changes, according to likely predictors, the mosquito will be able to survive at both higher latitudes and higher elevations, and more people will be exposed to malaria (Epstein 1998). Within the western United States, recent studies on the plague (Parmenter et al. 1999) and hantavirus pulmonary syndrome (Engelthaler et al. 1999) have indicated the potential impact of climate variability on regional diseases.

Research within the climate and health arena contains uncertainty. Researchers cannot be certain to what extent climate conditions will change. Given current practices, Global Circulation Models (GCM's) are able to predict worldwide climate conditions in the future, and work in concert with regional models. However, the extent of climate change will differ around the world, with some regions experiencing more extreme changes in climate conditions than others (Chan 1999). Therefore, diseases will not be impacted uniformly around the world. Also, as the climate changes, the vulnerability of populations may change (IPCC). People will adapt, and the impact may not be as negative as previously thought.

A major driving force of climate variability within the United States, as well as around the world, is the El

Niño-Southern Oscillation (ENSO). As the Southern Oscillation Index fluctuates between negative (El Niño) and positive (La Niña) values, atmospheric circulation and sea surface temperatures change, and some regions receive more precipitation than usual while others experience drier than average conditions. With the shift in climate conditions, research shows that the incidence of diseases associated with rainfall changes as well, with an increase in incidence of diseases found in the Southwest associated with El Niño conditions (Parmenter et al. 1999; Engelthaler et al. 1999).

Growing concern over climate variability and change and its impact on disease has led to national research initiatives to examine possible implications. A National Assessment on the Potential Consequences of Climate Variability and Change for the Nation has been completed. This report summarizes the possible effects of climate change and variability on various sectors, including human health, urban areas, water quality and availability, and energy supplies. The vulnerability of the various sectors to climate variability in different regions of the United States was determined and reported. In addition, several "Regional Assessments" of climate impacts have been conducted, including a study in the Southwest. The research in this thesis was completed as part of one of these, the Climate Impact Assessment for the Southwest Project (CLIMAS).

1.3 Thesis Structure

The following chapters outline the research that was conducted to explore climate and valley fever, and to develop a predictive incidence model. The thesis is structured around two stand-alone journal articles. The first is a literature review paper that has been accepted for publication in the journal Aerobiologia (Kolivras et al. 2001). The second paper will be submitted to an appropriate journal, and it comprises exploratory data analyses and model development of relationships between climate and valley fever. Finally, the thesis is summarized with a set of brief concluding remarks.

Chapter 2 - Previous Research on Climatic Variability and Incidence of Valley Fever

2.1 Introduction

Coccidioidomycosis, commonly known as valley fever or cocci, is caused by *Coccidioides immitis* (*C. immitis*), a fungus that grows in the soil of limited regions in the United States, as well as portions of Central and South America. Both humans and other mammals, such as dogs and cattle, are susceptible to the disease. Endemic regions within the United States (Fig. 2.1) include Kern County in the San Joaquin Valley of California; Pima, Pinal, and Maricopa counties of Arizona; and a small portion of Texas which runs east from the southeast corner of New Mexico to slightly beyond Laredo (Maddy 1965)

It has been documented that there is a relationship between outbreaks of valley fever and climatic conditions (Maddy 1957; Hugenholtz 1957; Maddy 1958). The fungus is sensitive to climate variability, and responds to changes in moisture and temperature. This paper is a review of previous research that has discussed the relationship between valley fever and climate. Introductory information on *C. immitis* and valley fever is followed by an overview

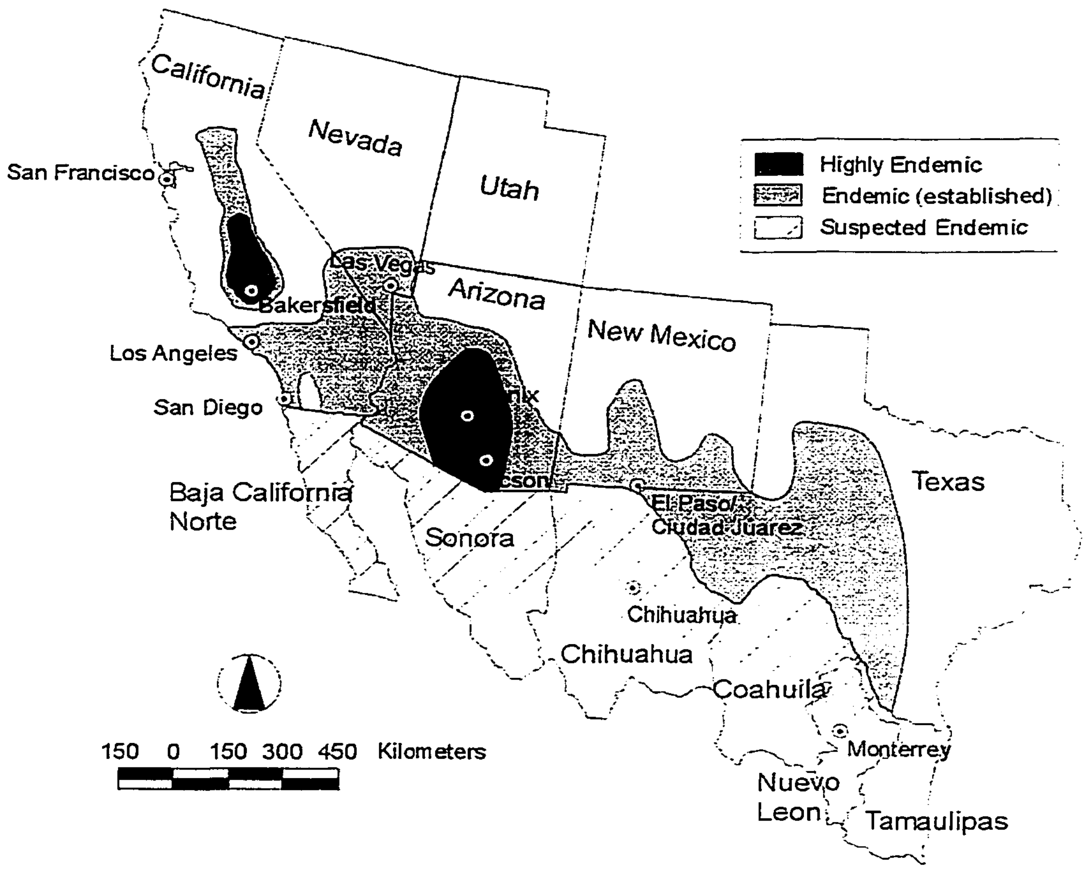

Fig. 2.1. Areas of the United States and northern Mexico that are considered endemic for valley fever.

of the existing state of knowledge regarding climate and the disease. I conclude with recommendations for future research that will lead to an improved understanding of the relationship between climate and valley fever.

The majority of previous studies were conducted several decades ago, and focused mainly on the distribution of *C. immitis* and an understanding of the different phases of the lifecycle, and other aspects of the disease. In most cases, only a passing reference is made to the role of climate in the fungus' lifecycle and subsequent outbreaks of valley fever. A few studies outlined the climatic characteristics of the study area or attempted to create conditions similar to the external environment in a laboratory, but little has been done quantitatively shows the presence or absence of, a specific relationship between climatic conditions and incidence of valley fever.

2.1.1 Lifecycle of *Coccidioides immitis*

A brief summary of the lifecycle of the fungus is useful for understanding the link between climate conditions and valley fever. *C. immitis* is considered to be a dimorphic fungus, given that its lifecycle consists of two different phases (Fiese et al. 1955) (Fig. 2.2). In the soil, *C.*

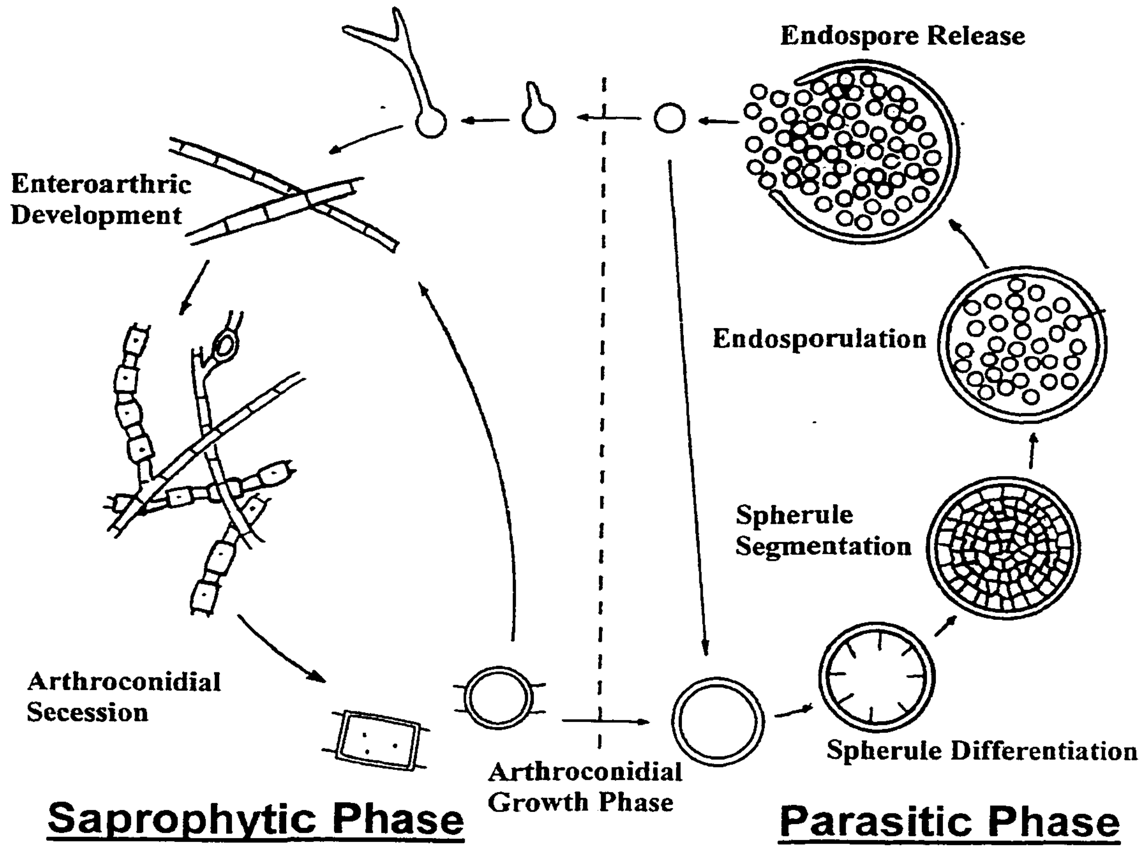

Fig. 2.2. *C. immitis* exists in both saprophytic (left) and parasitic (right) phases.

immitis exists in the saprophytic phase. Microscopic fungal spores called arthroconidia grow into long hyphae (strands), in which brittle, sterile cells separate pieces of the viable fungus. With moisture, the hyphae grow into large mats within the soil. When the soil dries, cells in hyphae encyst and form individual spores. Some portions of the live fungus remain in the soil continuing the saprophytic phase, while other spores become airborne. Once a host breathes in a spore, the parasitic phase of *C. immitis* begins. Spherules within the lung reproduce by filling with endospores. Once filled, the spherule bursts and endospores are released into the tissue. Each individual endospore develops into a spherule and repeats the process of filling with endospores. In this manner, the fungus is able to reproduce rapidly in the tissue, until the host's immune system suppresses the fungus or the host eventually dies.

2.1.2 Effect on Populations

Valley fever cannot be spread from person to person, and once a person has been infected with valley fever they gain, in most cases, lifelong immunity to the disease (Pappagianis 1988). Infections are most likely during dry, dusty periods, when arthrospores from the fungus become airborne and can be inhaled (Rutherford 1996). The majority of the people infected (60%) either presents no symptoms, or experience mild, cold-like conditions (Smith et al. 1946b). Some may endure a variety of flu-like symptoms that usually appear after an incubation period of one to three weeks (Smith 1946; Stevens 1995). Of those infected by *C. immitis*, about one percent experience a disseminated form of the disease when the spherules enter the bloodstream and spread beyond the lungs (Einstein 1992). Disseminated valley fever can express itself with a wide variety of conditions. Lesions may occur on organs outside of the pulmonary system, as well as on the skin; bones and joints may be damaged (Fiese 1958). The most severe form of the disseminated disease is coccidioidal meningitis, the mortality of which is essentially one hundred per cent when produced by valley fever (Fiese 1958).

Certain age groups and ethnic backgrounds are more vulnerable to valley fever. Although people of any age are susceptible to valley fever, the very young and the very old often experience the worst cases (Einstein 1992). Studies show people under the age of five and over the age of fifty who acquire valley fever are more likely to experience disseminated cases (Pappagianis 1988). These groups appear to be more vulnerable to the disease, as their immune systems are less resilient and less able to resist infection. Pappagianis (1988) reports a "disproportionate representation of certain ethnic groups among the cases of disseminated" valley fever. Studies have shown that blacks, Asians, Mexicans, Filipinos, and Native Americans are more likely to experience a severe form of valley fever than whites. While there may be a genetic tendency for different ethnic groups to experience differences in severity, it is possible that in the past people of non-European descent lived or worked in environments in which exposure to the fungus was more likely. Adult white females are less likely to have the disseminated disease than adult white males (Pappagianis 1988).

Occupation is also a factor in the occurrence of valley fever. Those working outside, including construction and agricultural workers, are more likely to be exposed to the fungus (Johnson 1981). Archaeologists also are frequently exposed to the fungus when conducting research in endemic regions (Werner and Pappagianis 1973).

Although most people infected with valley fever do not need to seek medical care, treatment of serious cases can be costly, both directly through medical care and indirectly, through lost worker-hours. On average, valley fever treatment in the United States costs $9 million annually, and results in almost a million person-days of labor (Pappagianis 1980). A 1977 outbreak in California cost approximately $2 million (Pappagianis 1980). Another outbreak in California, which lasted from 1991 to 1994, cost an estimated $66 million in treatment, hospitalization, and lost wages (Jinadu 1995).

2.2 Literature Review

2.2.1 Background Information on Climate and *C. immitis*

There is documented evidence relating outbreaks of valley fever and climatic conditions. *C. immitis* is sensitive to climate variability, and responds to changes in moisture and temperature. Growing concern over climate variability and change, and its impact on human health, has led to national research initiatives to examine possible implications. Valley fever is an emerging, infectious disease that could be highly influenced by climate variability and change, thus an improved understanding of its relationship to climate conditions is important.

Previous studies have suggested a relationship between the incidence of valley fever and climatic conditions. Temperature, precipitation, humidity, wind, and the occurrence of dust storms have been shown to affect either the growth of *C. immitis* and/or the distribution of the arthrospores.

Maddy (1965) has determined that endemic areas share certain climatic characteristics that appear to be most favorable to the growth of *C. immitis*. The average mid winter temperature is usually greater than 2 degrees Celsius, the average mid summer temperature is usually greater than 27 degrees Celsius, and the average annual rainfall is usually between 127 and 508 millimeters (Maddy 1965). These values vary slightly by report, but in general they characterize the highly endemic regions of the United States. The same characteristics are also indicative of much of the Lower Sonoran Life Zone, the distribution of which is very similar to that of the endemic region (Maddy 1957).

2.2.2 Precipitation and *Coccidioides immitis*

The role of precipitation in the lifecycle of *C. immitis* is two-fold: the fungus requires moisture to complete its lifecycle, and the presence of moisture in the soil decreases the amount of dust and airborne arthrospores (Pappagianis 1980). *C. immitis* requires a sufficient amount of water, but if conditions are too moist, competitors may prevail (Reed 1960). After rains, the fungus grows rapidly until the soil dries or until competitors stifle its growth (Maddy 1964; Reed 1960). After the soil dries, wind or another disturbance, such as digging or construction, break apart the hyphal chains. The arthrospores may then be dispersed and cause infections if they are inhaled.

The total amount of rainfall appears less important than precipitation effectiveness (Maddy 1964). Precipitation effectiveness, a measure of soil moisture persistence, can be determined by examining factors such as runoff, evaporation, temperature, and vapor pressure, as well as the soil type (Maddy 1964). *C. immitis* requires moist soils for growth, but for winds to distribute the fungus, the soil must dry out at some point during the year.

Very low rainfall, as well as annual rainfall in excess of 500 mm, decreases the prevalence of *C. immitis* in the soil (Reed 1960). The Mohave and Sonoran Deserts of California receive approximately 76 mm of rain annually, too dry for *C. immitis* (Maddy 1958). Coincidentally, increased rainfall at the eastern limits of the endemic zone in Texas enables competitive species to thrive (Maddy 1958).

2.2.2.1 Seasonality of Precipitation

Previous studies have reported from soil samples collected in California the times of the year when moisture conditions appear most favorable for the growth of the fungus. In their analysis of soil samples from the southwestern San Joaquin Valley, Egeberg and Ely (1956) discovered a seasonal variation of the distribution of *C. immitis* in its saprophytic phase. More samples tested positive for *C. immitis* at the end of the wet season than at the end of the dry period. Moreover, all positives collected at the end of the wet season were removed from surface soil. No positives were detected below the surface. In another study, the fungus was not recovered from any of the samples collected in August and December, during and at the end of the dry season in California (Elconin 1957). Further studies in California found that the peak time period for recovering *C. immitis* from the soil was approximately six weeks following the last rain (Elconin 1964). Figure 2.3 illustrates the relationship between precipitation and valley fever incidence in the southern San Joaquin Valley in California. California receives the majority of its precipitation during winter, and has a single peak in incidence in late fall and early winter following the summer dry season. Pima County, Arizona, on the other hand, experiences a bimodal precipitation pattern, and therefore the annual cycle of valley fever incidence is more complex than that of California (Fig. 2.4). A small peak in incidence is experienced in early summer following a dry spring, while the highest annual incidence is experienced in November and December following the summer monsoon and dry autumn.

Maddy (1965) conducted a similar study in south central Arizona, and found that the majority of the *C. immitis*-positive samples were collected between September and December following the summer rainy period. This study shows that *C. immitis* is most often recovered from the soil

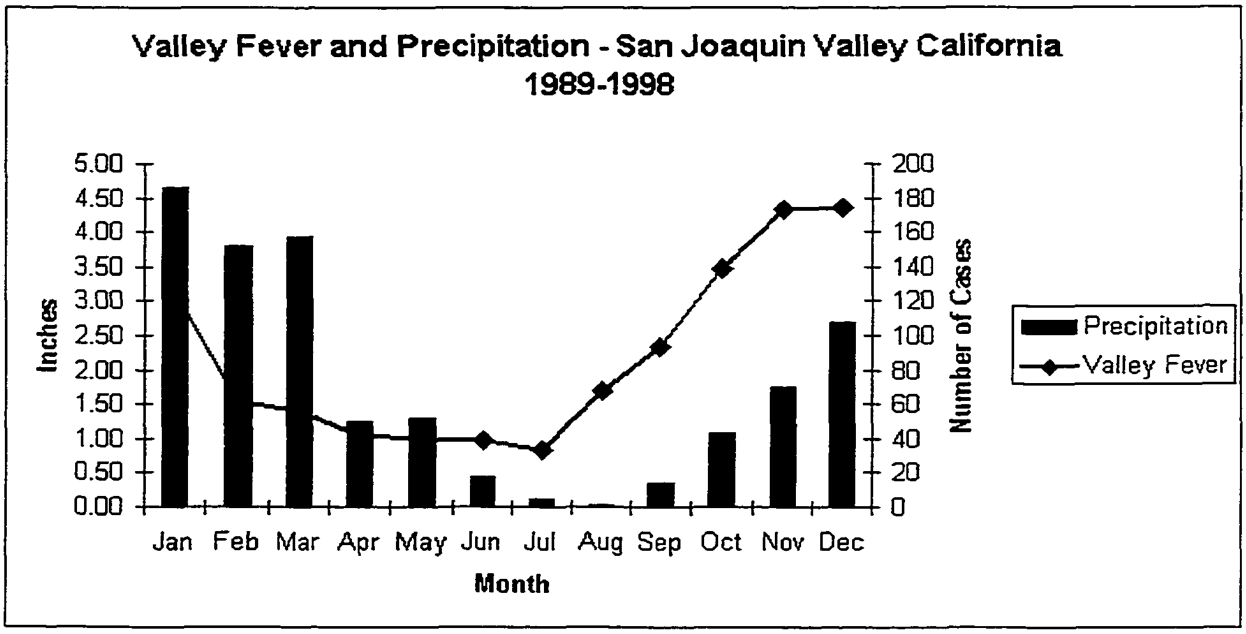

Fig. 2.3. California's pattern of precipitation and valley fever incidence. (Source: National Climatic Data Center and Arizona Department of Health Services)

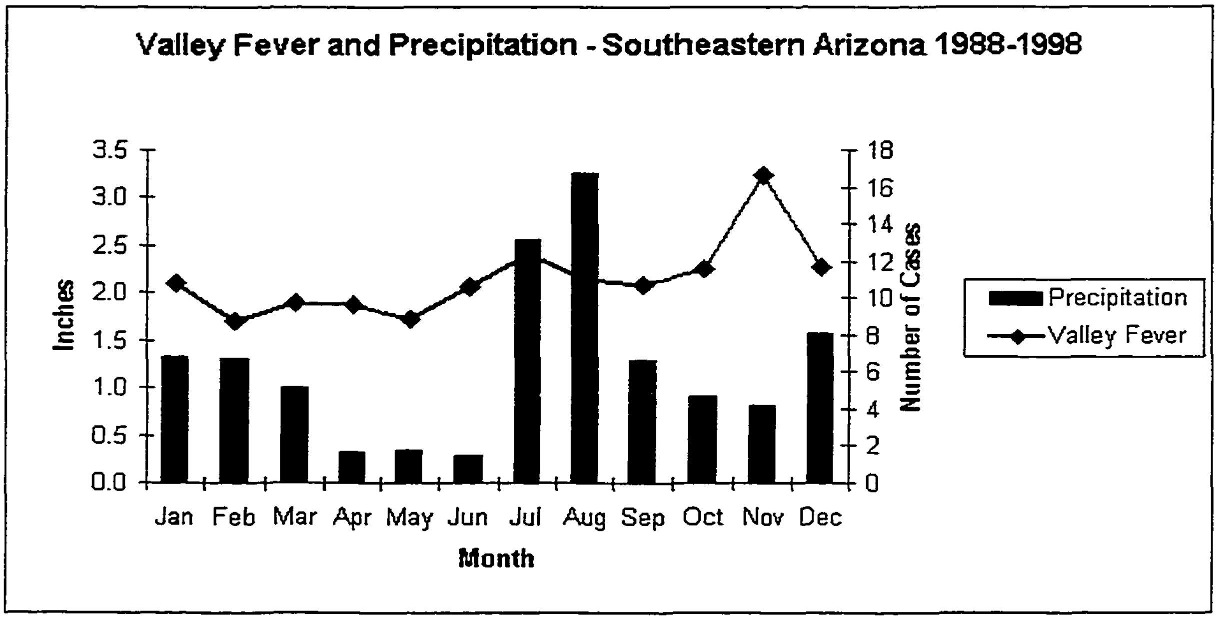

Fig. 2.4. Arizona's bimodal precipitation pattern, and corresponding pattern of valley fever incidence. (Source: National Climatic Data Center and California Department of Health Services)

in the time period following the rainy season, and more rarely during the hot, dry season.

2.2.2.2 Variability of Precipitation

Researchers examining the variability of valley fever incidence have often also noted the variability in climatic conditions. A study of valley fever incidence at four Army air fields in the San Joaquin Valley by Smith and coworkers (1946a) showed a relationship between precipitation and incidence. The highest number of cases occurred during the dry summer and fall, while the lowest number occurred during winter and spring. An increase in incidence was found to follow a particularly wet winter. The study showed also that the effect of rainfall was reflected in the month in which it occurred as well as the following month.

Maddy (1965) noted the majority of human infections seem to occur during the windy, dusty period following the wet season. Although the majority of California's rainfall occurs in winter, it has been noted that summer rains in California, coupled with high temperatures, seem to reduce the incidence of the disease during the following fall and winter (Jinadu 1995). It has also been shown that heavy rains in February and March are followed by an increased number of cases in the fall (Stevens 1995).

A study by Hugenholtz (1957) concerned the relationship between the incidence of valley fever and several climatic variables in Arizona, namely temperature, rainfall, and dust storms. An examination of hospital admissions records at Williams Air Force Base in Maricopa County from 1952 to 1956, for example, showed two annual peaks in valley fever incidence, one in July and a second in October or November (Hugenholtz 1957). Months with highest incidence coincided with months having the lowest rainfall. Hugenholtz employed quantitative techniques in the study, correlating temperature, dust storm incidence, or total rainfall, with valley fever incidence. The study did not find a strong relationship between rainfall and incidence, but found stronger relationships with temperature and dust storms. Based on the findings however, Hugenholtz (1957) concluded that it is possible to predict lower infection rates during a season if the preceding wet period was drier than normal (Hugenholtz 1957). For example, infection rates should be lower in the spring and summer following a relatively dry winter, and a drier than usual July and August should be followed by fewer infections in fall (Hugenholtz 1957). Hugenholtz commented that his "remarks have been largely theoretical and based on an incomplete study, but they may serve to stimulate studies by other investigators."

In the early 1990s, California experienced an epidemic of valley fever that was linked to variability in precipitation. Jinadu (1995) reported that the epidemic followed five years of drought in California. This review of the epidemic was based on a descriptive analysis of the rainfall conditions leading up to and during the outbreak. February and March of 1991 through 1994 had approximately double the normal amount of rainfall, and Jinadu (1995) commented that these "intense rains caused an abundant growth" of the fungus in the soil. After drying, the soil was disturbed by winds, and *C. immitis* spores were released into the air causing a much greater number of cases than normal, particularly in Kern County, California.

2.2.3 Temperature and *Coccidioides immitis*

Soil sterilization is thought to be very important in the lifecycle of *C. immitis*. During prolonged periods of hot, dry conditions, the surface of the soil is partially sterilized and many competitors are removed, but *C. immitis* arthrospores remain viable below the surface (Maddy 1965; Reed 1960). When rain falls, conditions in the surface soil eventually approach the ideal for the growth of the fungus. It returns to the surface layer, which contains few competing organisms (Maddy 1957).

2.2.3.1 Seasonality of Temperature

Several studies examined the conditions in which *C. immitis* survives in its natural environment. Plunkett and Swatek (1957) conducted a study to isolate the fungus from the soil in an area in California where archaeology students were infected, and examine the seasonality of the fungus (Plunkett 1957). *C. immitis* was recovered during every month from a depth of 100 mm below the surface, but was not found on the surface during August, October, and November (Plunkett 1957). Data for September were not listed. Soil temperatures 25 mm below the surface were recorded, and the high temperature at that depth was found to be 60.5 °C (Plunkett 1957). Temperatures between 49 °C and 54.4 °C were often recorded during the time of the study (Plunkett 1957). It was noted that moisture was not evident in the soil at the 100-150 mm level during August, September, and October (Plunkett 1957). *C. immitis* was able to survive at this depth in spite of the dry conditions, but was not able to survive on the surface at this time of year, possibly due to the high surface soil temperatures.

Maddy (1965) conducted a similar study in Arizona. Over a two-year period, the majority of *C. immitis*-positive samples were collected between September and December (Maddy 1965). Temperatures at a depth of 12.7 mm below the surface often ranged from 60-70 °C for almost 100 days during the summer (Maddy 1965). Maddy commented that "surface soil temperatures were too high in the early summer to be favorable for the growth of many microorganisms."

2.2.3.2 Variability of Temperature

Research has been conducted within the laboratory to determine the hardiness of *C. immitis*. Overall, the study showed the adaptation of arthrospores to a wide variety of conditions. Friedman et. al. (1956) studied the survival characteristics of one strain of *C. immitis* at different temperatures and different relative humidities within the laboratory, finding arthrospores were able to survive for six months under a wide variety of conditions (-15 °C to 37 °C, and a wide range of relative humidities). The only situation unfavorable to the spores was the combination of high temperature (37 °C) and low relative humidity (10%) (Friedman 1956). Six months elapsed at these conditions, however, before all of the spores died, thus the fungus is able to survive for short periods in extreme conditions. This particular combination of temperature and relative humidity is characteristic of the endemic region in general, but both temperature and relative humidity change on a diurnal and seasonal basis.

2.2.4 Dust Storms

The arthrospores are distributed easily by wind, linking dust storms to outbreaks of valley fever. Two epidemics in particular have been the result of dust storms. In December of 1977, a dust storm that blew through Kern County, California carried dust and *C. immitis* spores to the north and west sparking an epidemic in which the number of cases in the six months following the storm exceeded the annual number of cases in any year in

California up to that time (Pappagianis 1978). Rainfall several days after the dust storm prevented the epidemic from being any worse (Pappagianis 1978). An outbreak of valley fever following the Northridge earthquake was the result of dust clouds that were generated from landslides during and after the quake (Schneider 1997). A study of the occurrence found that those who reported being physically within a dust cloud were three times more likely to be diagnosed with valley fever than those that were not as obviously exposed to dust and arthrospores (Schneider 1997).

Prior research has addressed dust control and at the same time, the control of outbreaks of valley fever. In the 1940s, four Army air fields in the San Joaquin Valley experimented with dust control by spreading refined oil on athletic fields (Smith 1946a). Other methods of dust control included paving roads and vegetating lawns and fields (Smith 1946a). A combination of these methods produced a one half to two thirds decrease in infection rates by reducing the amount of dust and *C. immitis* arthrospores distributed by wind and disturbed by activity (Smith 1946a).

2.2.5 Non-Climatic Environmental Factors

Other environmental factors in addition to climate conditions affect the growth of *C. immitis* and valley fever incidence. Elconin et al. (1964) has indicated that a deposition of salts near the surface of the soil creates favorable conditions for the growth of *C. immitis*. Increased surface soil salinity can work in conjunction with high surface temperatures to partially sterilize the soil, killing competing microorganisms while allowing *C. immitis* to survive (Egeberg and Ely 1956; Elconin et al. 1964).

Another important factor related to the growth of the fungus is the relationship with other organisms in the soil. *C. immitis* can often be isolated near or within pack-rat burrows (Lacy and Swatek 1974). This environment provides organic material for the fungus to consume.

Finally, human activity that disturbs the soil can facilitate the dispersal of the fungus. Farming, construction activity, and archaeological surveys have been associated with increased incidence of valley fever (Pappagianis 1988).

2.3 Conclusion and Future Research

Little research examining the role of climate variability in the occurrence of valley fever has been performed since the 1950s and 1960s. Of the studies during that period, only a few compared climate and incidence data. In particular, the study by Hugenholtz (1957) looked for a correlation between such information, but analyzed only fourteen years of data for a specific area. Although there is a general understanding of the climatic characteristics of the endemic region, the specific conditions that may result in an outbreak of valley fever are not well understood.

Although the data are in some ways problematic (given different reporting techniques and a varying incubation period), long records of valley fever incidence are available. A quantitative analysis of incidence data in conjunction with climate data, such as temperature, precipitation, wind speed, and relative humidity is recommended. Analysis of multivariate climate data and valley fever incidence data can then be used to develop models of *C. immitis'* response to climate. A predictive model will be particularly useful to health care providers and government health services.

Chapter 3 - Relationships Between Climate and Valley Fever in Pima County, AZ, 1948-1998

3.1 Introduction

3.1.1 Background

Coccidioidomycosis, commonly known as valley fever or cocci, is a disease endemic to the western hemisphere. It is found in limited regions in the United States, as well as areas in Central and South America, and is caused by *Coccidioides immitis* (*C. immitis*), a soil-dwelling fungus that is sensitive to climate conditions. The most highly endemic regions within the United States (Fig. 3.1) include Kern County in the San Joaquin Valley of California (hence the name Valley Fever) and Pima, Pinal, and Maricopa counties of Arizona (Maddy 1965).

Infections first occur in the lung, when the fungus becomes airborne, and is inhaled by a host. Both humans and other mammals, such as dogs and cattle, are susceptible to the disease. The majority of the people infected (about 60%) either presents no symptoms, or experience mild, cold-like conditions (Smith et al. 1946b). Some may endure a variety of flu-like symptoms, including fever, coughing, and chest pain, which usually appear after an incubation

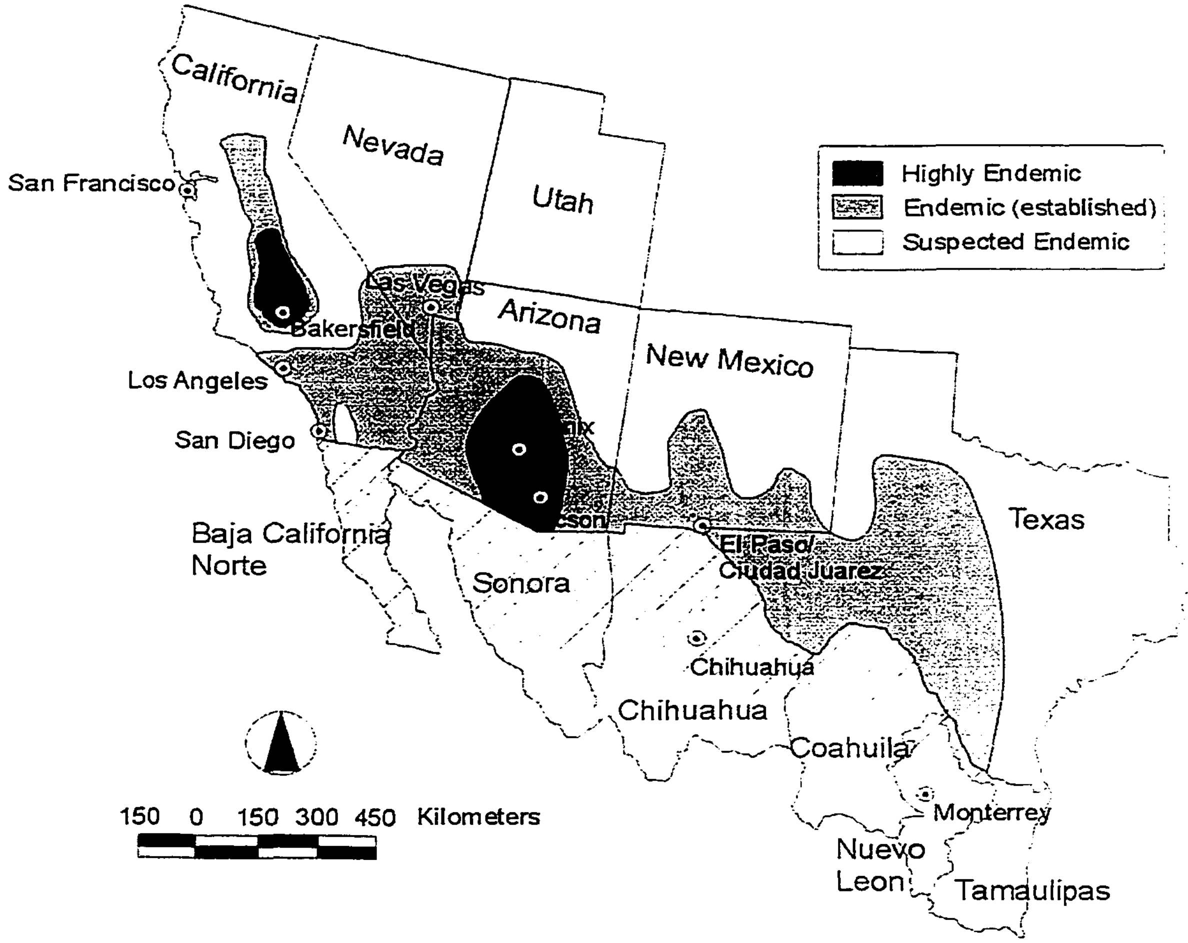

Fig. 3.1. Areas of the United States and northern Mexico that are considered endemic for valley fever.

period of one to three weeks (Smith et al. 1946b; Stevens 1995). Of those infected by *C. immitis*, about one percent experience a disseminated form of the disease when the fungal spores enter the bloodstream and spread beyond the lungs (Einstein 1992). Disseminated valley fever can express itself with a wide variety of conditions, including joint damage, skin lesions, and potentially fatal meningitis.

Certain age groups and ethnic backgrounds are more vulnerable to valley fever. Although people of any age are susceptible to valley fever, the very young and the very old often experience the worst cases (Einstein 1992). Studies show cases of valley fever in people under the age of five and over the age of fifty are more likely to experience disseminated cases (Pappagianis 1988). These groups appear to be more vulnerable to the disease, as their immune systems are less resilient and less able to resist infection. Pappagianis (1988) reports a "disproportionate representation of certain ethnic groups among the cases of disseminated" valley fever. Studies have shown that blacks, Asians, Mexicans, Filipinos, and Native Americans are more likely to experience a severe form of valley fever than whites. While there may be a genetic tendency for different ethnic groups to experience differences in severity, it is possible that in the past people of non-European descent lived or worked in environments in which exposure to the fungus was more likely. Adult white females are less likely to have the disseminated disease than adult white males (Pappagianis 1988).

Occupation is also a factor in the occurrence of valley fever. Those working outside, including construction and agricultural workers, are more likely to be exposed to the fungus (Johnson 1981). Archaeologists also are frequently exposed to the fungus when conducting research in endemic regions (Werner and Pappagianis 1973).

3.1.2 Lifecycle of *C. immitis*

A brief summary of the lifecycle of the fungus is useful for understanding the link between climate conditions and valley fever. *C. immitis* is considered to be a dimorphic fungus, meaning that its lifecycle consists of two different phases (Fiese et al. 1955) (Fig. 3.2). In the soil, *C. immitis* exists in the saprophytic phase. Microscopic fungal spores called arthroconidia grow into long hyphae (strands), in which brittle, sterile cells

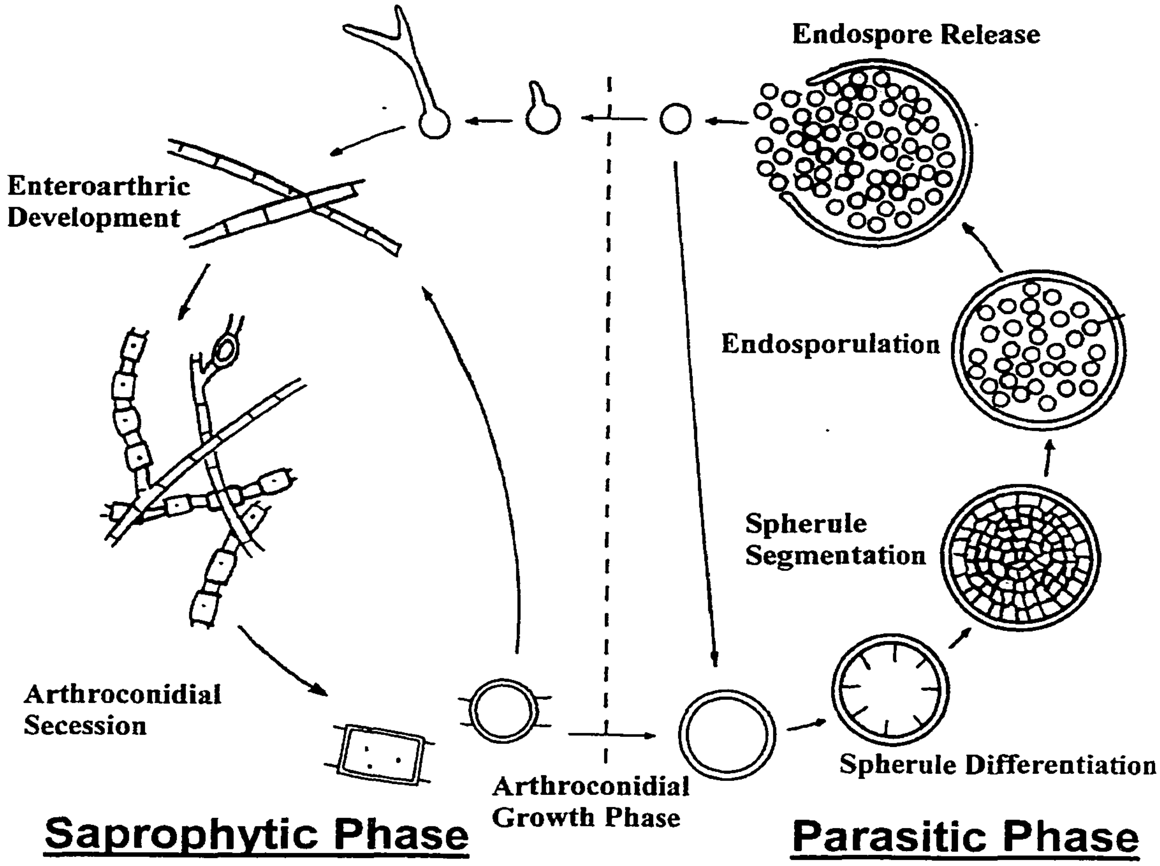

Fig. 3.2. *C. immitis* exists in both saprophytic (left) and parasitic (right) phases. (Adapted from Fiese 1958.)

separate pieces of the viable fungus. With moisture, the hyphae grow into large mats within the soil. When the soil dries, cells in hyphae encyst and form individual spores. Some portions of the live fungus remain in the soil, while other spores become airborne. Once a host inhales a spore, the parasitic phase of *C. immitis* begins. Spherules within the lung reproduce by filling with endospores. Once filled, the spherule bursts and endospores are released into the tissue. Each individual endospore develops into a spherule and repeats the process of filling with endospores. In this manner, the fungus is able to reproduce rapidly in the tissue, until the host's immune system suppresses the fungus or the host eventually dies.

3.1.3 Climate Relationships

It is generally understood that, given *C. immitis'* response to moisture within the soil, a relationship exists between climate conditions and valley fever incidence (Hugenholtz 1957; Maddy 1957; Maddy 1958; Kolivras et al. 2001). However, little research examining the role of climate variability in the occurrence of valley fever has been performed since the 1950s and 1960s. Most studies anecdotally mention the presence of a link between climate and incidence, but they did not quantitatively examine that relationship. Kolivras et al. (2001) reviewed the existing literature, and found that of the studies during that period, only a few compared climate and incidence data. In particular, the study by Hugenholtz (1957) looked for a correlation between such information, but only fourteen years of incidence data were available at that time.

Previous studies have shown that precipitation and temperature are important in the lifecycle of *C. immitis* (Hugenholtz 1957; Maddy 1957; Maddy 1958; Kolivras et al. 2001). The role of precipitation in the lifecycle of *C. immitis* is two-fold: the fungus requires moisture to complete its lifecycle, but a period of dry conditions enables the fungus to become airborne (Pappagianis 1980). *C. immitis* requires a sufficient amount of water, but if conditions are too moist, competitors within the soil may prevail (Reed 1960). After rains, the fungus grows rapidly until the soil dries or until competitors stifle its growth (Maddy 1964; Reed 1960). After the soil dries, wind or another disturbance, such as digging or construction, liberate the fungal spores, which may then be dispersed and cause infections if they are inhaled. *C. immitis*, like all fungi, requires the presence of moisture to complete its lifecycle. However, in order for the fungus to become airborne and cause infections, the soil must dry at some point during the year. Therefore, it is hypothesized, that a cycle of wet and dry conditions is necessary for outbreaks of the disease to occur.

Temperature also plays a vital role in the growth of *C. immitis* through surface soil sterilization. It is hypothesized that during prolonged periods of hot, dry conditions, the surface of the soil is partially sterilized and many competitors are removed, but *C. immitis* spores remain viable below the surface (Maddy 1965; Reed 1960). When rain falls, conditions in the surface soil eventually approach the ideal for the growth of the fungus. It is thought that *C. immitis* then returns to the surface layer, which contains few competing organisms, and grows fairly rapidly in this more ideal environment (Maddy 1957). A subsequent dry period then allows the fungus to become airborne, and infections to occur. Although there is a general understanding of the climatic characteristics of the endemic region, and the conditions that are conducive to fungal growth, the specific conditions that may result in an outbreak of valley fever are not well understood.

3.1.4 Climatic Characteristics of Study Area

Presumably, the climate conditions in the endemic area represent those most favorable for the growth of *C. immitis*. Because of data availability, this study focuses on Pima County, which is located in south central Arizona in the Sonoran Desert. Characteristic of much of the endemic area, Pima County receives low annual precipitation on an annual basis (approximately 12 inches in Tucson), which is coupled with a wide range in diurnal and seasonal temperatures (Fig. 3.3). The region is characterized by a bimodal precipitation pattern, in which rainfall is received during the winter and summer, and is otherwise fairly dry. Winter precipitation is received mainly as a result of frontal systems that enter the southern portion of the United States, and is characterized by soaking rains that last several days. Following the northward retreat of frontal systems in spring is a dry foresummer period in which insolation and temperatures are high due to a lack of cloud cover. Summer precipitation occurs as a result of the North American monsoon, and is characterized by intense thunderstorms with high spatial and temporal variability in precipitation. Monsoon circulation is usually in place around the beginning of July, and typically lasts through

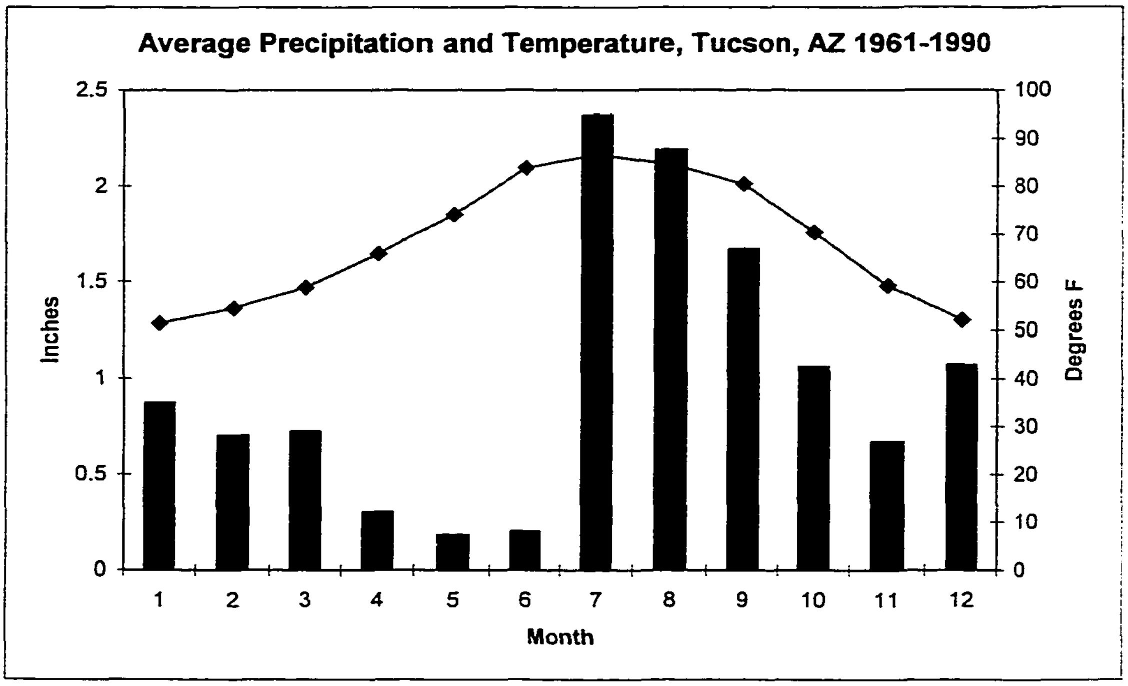

Fig. 3.3. Average precipitation and temperature, Tucson, Arizona.

mid-September. Following the end of the monsoon pattern, a relatively dry period is in place until the beginning of winter precipitation. These average patterns show large variability from year to year, and are affected in part by climate fluctuations such as the El Niño-Southern Oscillation.

The climate of Pima County is therefore conducive to high valley fever incidence when considered within the framework of the fungus' response to climate conditions. Hot, dry conditions during the spring and fall provide a setting during which competing organisms may not be able to survive in the soil. Soil moisture increases during the winter and summer periods of increased rainfall, enabling the fungus to grow within the soil, perhaps relatively free of competition. Finally, the soil dries again, permitting fungal spores to become airborne and infections to occur. Other environmental factors in Pima County, including soil type and salinity, also provide an environment favorable to the growth of the fungus. However, this study focuses on the association between climate conditions and incidence.

3.1.5 Overall Aims of Study

The broad aims of this research are twofold. The first goal is to improve our understanding of the basic relationships between climate and valley fever through exploratory data analysis. This portion consisted of bivariate correlation analyses as well as a compositing analysis of antecedent climate conditions. Using the understanding of climate and valley fever gained through the exploratory data analysis, our second goal was to develop monthly multivariate models to predict valley fever incidence based on current or forecast climate conditions.

3.2 Data

3.2.1 Valley Fever Data

This study focuses on Pima County, AZ, which has one of the highest rates of valley fever in the world, and is experiencing a rapid growth of susceptible populations (Galgiani 1999). The long data record was also an important factor in choosing Pima County data for the analysis. Maricopa County is also endemic to valley fever, however, incidence data were not readily available at the time this study began. Although valley fever incidence is also high in Kern County, California, the existing available monthly incidence data record (1989-1998) is not long enough for the analysis conducted in this study. Monthly valley fever incidence data, by month of estimated disease onset, for Pima County for 1948-1998 were obtained from the Arizona Department of Health Services (ADHS).

Ideally for this study, we would analyze the relationship between valley fever and climate using actual fungal count data from the soil or air rather than incidence data. Unfortunately, fungal count data are currently unavailable for several reasons: The fungus is very difficult to isolate in the soil, and the culturing process requires special laboratory biosafety facilities and is very time-intensive. As a result, there are no time-series of spore data amenable to climatic analysis. Instead, we use incidence data, which are several steps removed from the effect of climate (Fig. 3.4). When climate conditions are right for the fungus to grow in high numbers in the soil and the soil then dries out, spores may be dislodged and become airborne. Following an airborne dispersal of *C. immitis* spores in which a host becomes infected, symptoms will appear after an incubation period of 14-21 days (Smith 1946b; Stevens 1995). If conditions

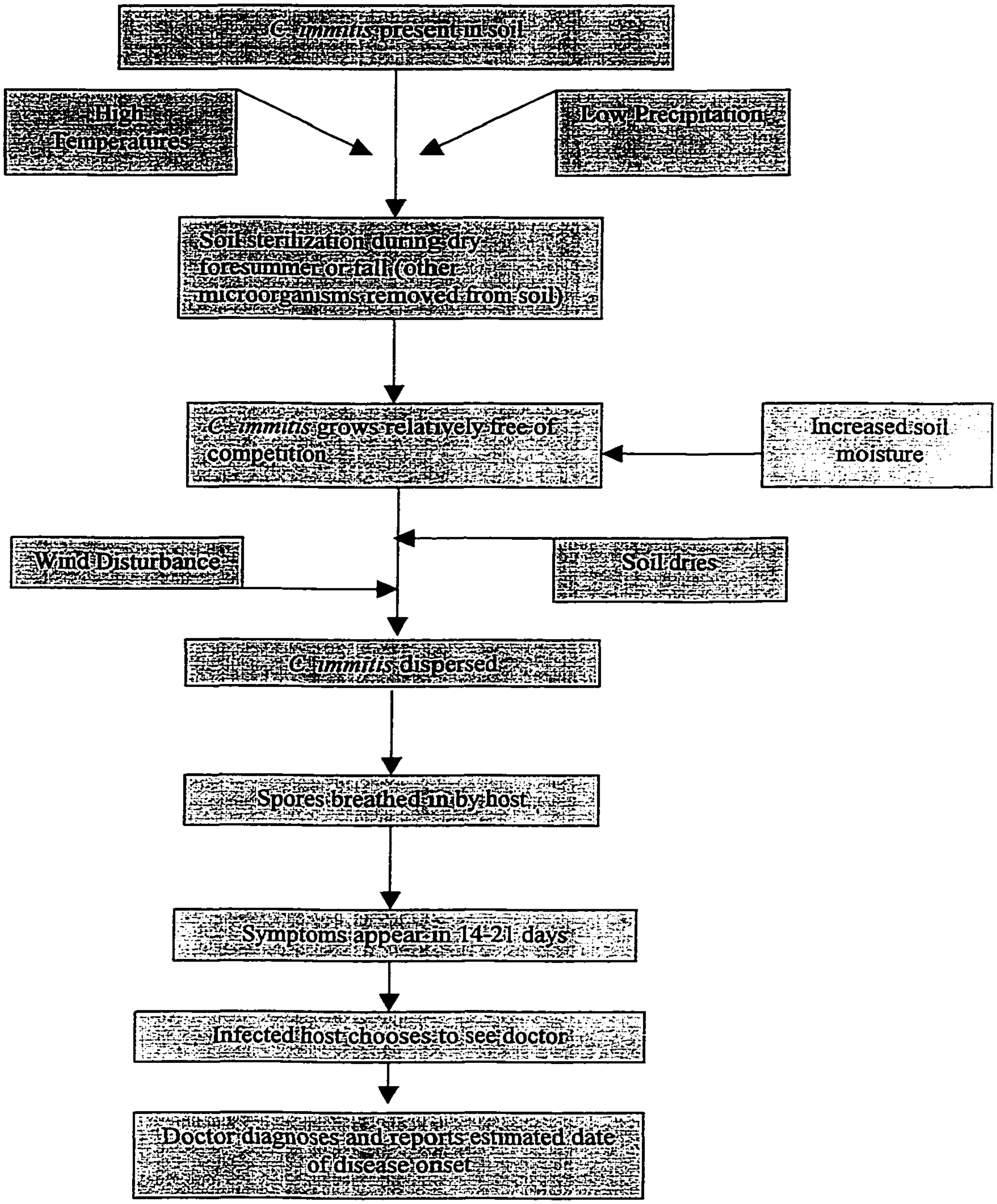

Fig. 3.4. Incidence data are several steps removed from the effects of climate conditions on fungal growth.

become severe, the infected person will visit a doctor. The physician then reports the estimated date on disease onset to ADHS. Also, the fungus is not evenly distributed across the endemic region. Rather, its distribution is spotty across the landscape; the fungus may be present in one area but not found just a short distance away (meters or tens of meters). Therefore, although climate conditions impact growth and dispersal of the fungus directly, incidence was used as a substitute of the fungus' response to climate.

There are concerns about the quality of the incidence data, and several points apparent in Figure 3.5 require attention. As shown by the graph, there are no available data for 1973-1979, decreasing the fifty-one year data record to forty-four years. Perhaps the major problem in the data record is the lack of a consistent reporting standard over time. The method of reporting cases of valley fever to the ADHS by doctors has changed many times over the past fifty years. Overreporting may explain the very high number of cases during the late 1950s and 1960s, but other interannual variability may still be dominated by reporting changes. The data from 1980-1998 are considered to be more trustworthy than the entire data record since

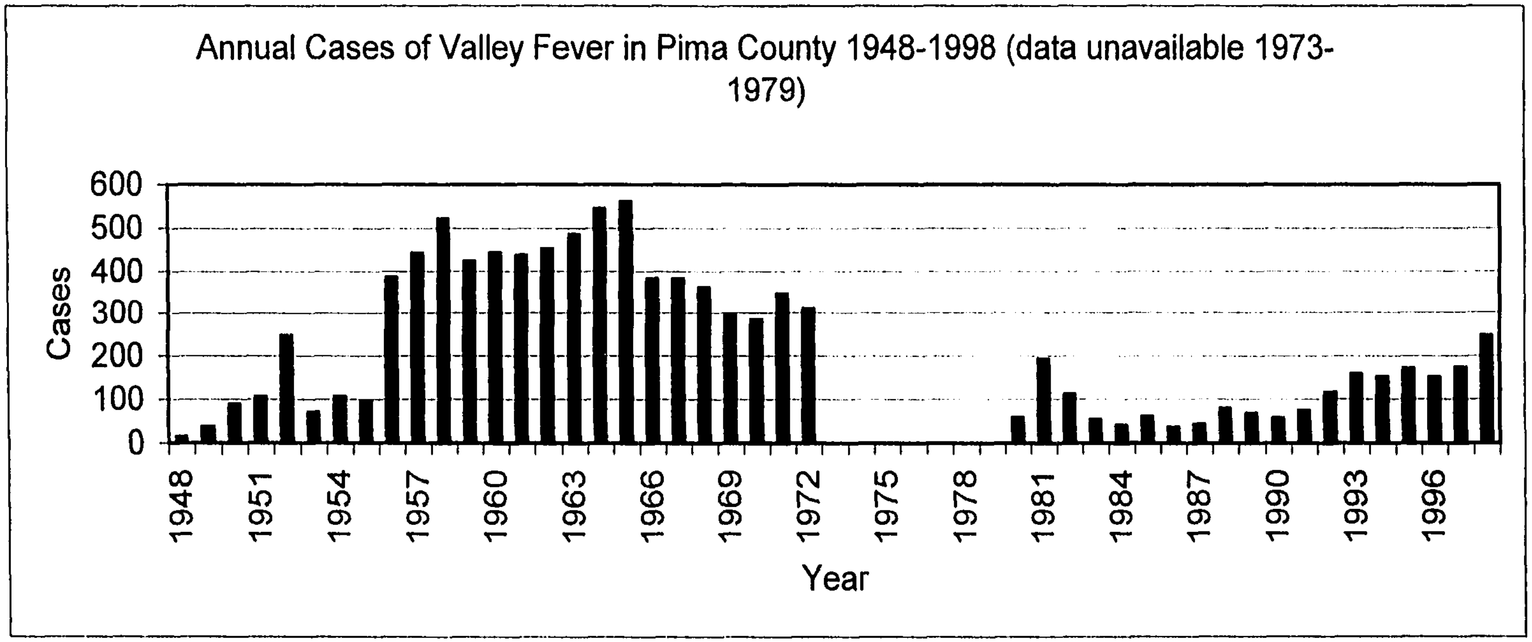

Fig. 3.5. Valley fever incidence Pima County, Arizona.

annual variation is less extreme during that time. Also, in the mid-1990s, reporting techniques were standardized. In addition, the number of susceptible people has changed over this time period, and soil disturbance due to development has varied as well. Both factors play a role in the unevenness of the time series. Our intent in this study is to identify the climatic component of variability over time, and the methodology for doing so is outlined in section 3 below.

3.2.2 Climate Data

Monthly climate data for southeastern Arizona (Climate Division 7) were obtained from the National Climatic Data Center (NCDC). In addition to temperature and precipitation, we used Palmer Drought Severity Index (PDSI) as a proxy for soil moisture since an appropriate measure for Pima County was not available for 1948-1998. The balance between wet and dry conditions in the soil is likely to affect the growth and distribution of *C. immitis*, and therefore PDSI was deemed a useful variable to include in the study. One caveat with the use of PDSI is that temporal autocorrelation is intrinsic to the index. The smoothing that is used to create the value means that the index does not change rapidly with changes in soil moisture conditions. Rather, the index changes slowly given temperature and precipitation patterns over a time period of several months. Also, the index was developed for semiarid and dry sub-humid climates, and its application in other climate regimes, including desert regions, may lead to erroneous results (Guttman 1991). For these reasons, PDSI was used for exploratory analysis, and not included in model development. Other climate data were acquired for an individual station, Tucson International Airport, from NCDC. Since 98% of Pima County's population resides in the Tucson metropolitan area (http://www.census.gov), it was acceptable to apply Tucson station climate data to countywide valley fever data. The station data included average daily maximum, minimum, and dew point temperatures and average daily wind speed. These daily data were averaged to produce monthly data to compare to the monthly incidence data.

3.3 Methodology

A quantitative analysis of incidence data in conjunction with climate data, including temperature, precipitation, and wind speed was performed. To understand the basic relationships between valley fever and climate, and to determine the most appropriate climate variables to include in the multivariate predictive model, an exploratory data analysis was performed in two steps. Initially, a bivariate comparison of climate variables and incidence was performed. Then, the climate conditions leading up to a month with particularly high or low incidence were examined through a compositing analysis. The results of the exploratory portion of the study guided the development of multivariate regression models to predict monthly incidence using antecedent climate conditions.

This portion of the study was conducted to understand the scale of action of *C. immitis*. The fungus exists at very fine spatial scales, however the climate data was acquired for a broad spatial scale, at the level of climate division. Incidence data was available at the county level. This spatial mismatch could be resolved by linking the spatially limited, but temporally refined climate model with a spatial model in order to develop a more complete predictive model.

3.3.1 Exploratory Data Analysis

3.3.1.1 Bivariate Analyses

The monthly climate variables included in the bivariate analyses were total precipitation, average, minimum, and maximum temperatures, dew point temperature, average wind speed, and the Palmer Drought Severity Index. For this analysis, valley fever incidence data from 1980-1998, standardized by Pima County population, were used. As previously mentioned, these data are considered to be more reliable than the entire long-term record.

The analyses were performed using lags of one through twelve months in order to determine the timing of the climate variable's influence on incidence. Temperature and precipitation impact the fungus as it grows in the soil, and ultimately then influence the dispersal of the fungus. The lags accounted for a delay in the impact of climatic conditions on the growth and dispersal of *C. immitis*. Incidence in a particular month was compared to each of the climate variables in the preceding months, up to a period of one year. The relationship was examined visually with scatterplots, and by calculation of correlation coefficients between variable pairs. Those climate variables and time lags that significantly influenced incidence were identified as potential input variables in the multivariate model.

3.3.1.2 Composite Analysis

In order to use the entire record of incidence data (1948-1998), the raw case counts were transformed to account for the changes in reporting methods over the time period. Incidence in each month was expressed as a percentage of the respective year's annual total (e.g., January 1983 as a percentage of total incidence in 1983). During any one particular year, it is likely that the same reporting standards were used, and the month-to-month variability is fairly accurate, even if the raw data is inconsistent over the time span of several years. The deviation from the mean monthly percentage of the annual total was then calculated for each month (e.g., January 1983 percentage above or below average percentage for all Januarys). The ten highest and lowest of these deviations were identified for each month. Deviations from mean climate conditions were calculated for the forty-eight months preceding months with high and low incidence. Composites of average deviation for the climate variables were constructed for months with a high and low percentage of annual incidence. As a result of these transformations, above or below antecedent climate conditions were compared to similarly above or below normal valley fever incidence, all values normalized by month.

3.3.1.3 Modeling Overview

To improve understanding of multivariate relationships between climate variables and incidence, and to provide the potential for forecasting disease outbreaks, multiple linear regression models were developed for each month. Candidate input variables were selected from the results of the exploratory data analyses, and screened using principal components analysis (PCA) to avoid collinearity. For each month, anomalous years were excluded from model development to ensure a normal distribution of incidence data. One anomalous year was excluded for six different months; anomalous years were not present in the other months, and therefore no years were excluded in the model development for those particular months. The models were designed to predict deviation from mean incidence, and were cross-validated on independent data.

3.4 Results and Discussion

3.4.1 Bivariate Analyses

As previously mentioned, this portion of the study was conducted using incidence data per 100,000 people for 1980-1998. The long-term record (1948-1998) is highly varied, and the quality of the data is less certain than more recent data.

3.4.1.1 Precipitation

The bivariate analysis shows that precipitation in October negatively influences valley fever incidence in both short term and long term time periods. A one-month lag as well as seven- through eleven-month lags show a higher correlation than other lag periods (Fig. 3.6). In other words, precipitation in October is negatively associated with incidence in November as well as the following May through September. Rainfall during this time period likely moistens the soil and the fungus does not become airborne easily. Precipitation in other months also influences incidence, but the relationship is not as apparent nor as consistent as that of October. Precipitation may be important on time scales longer than

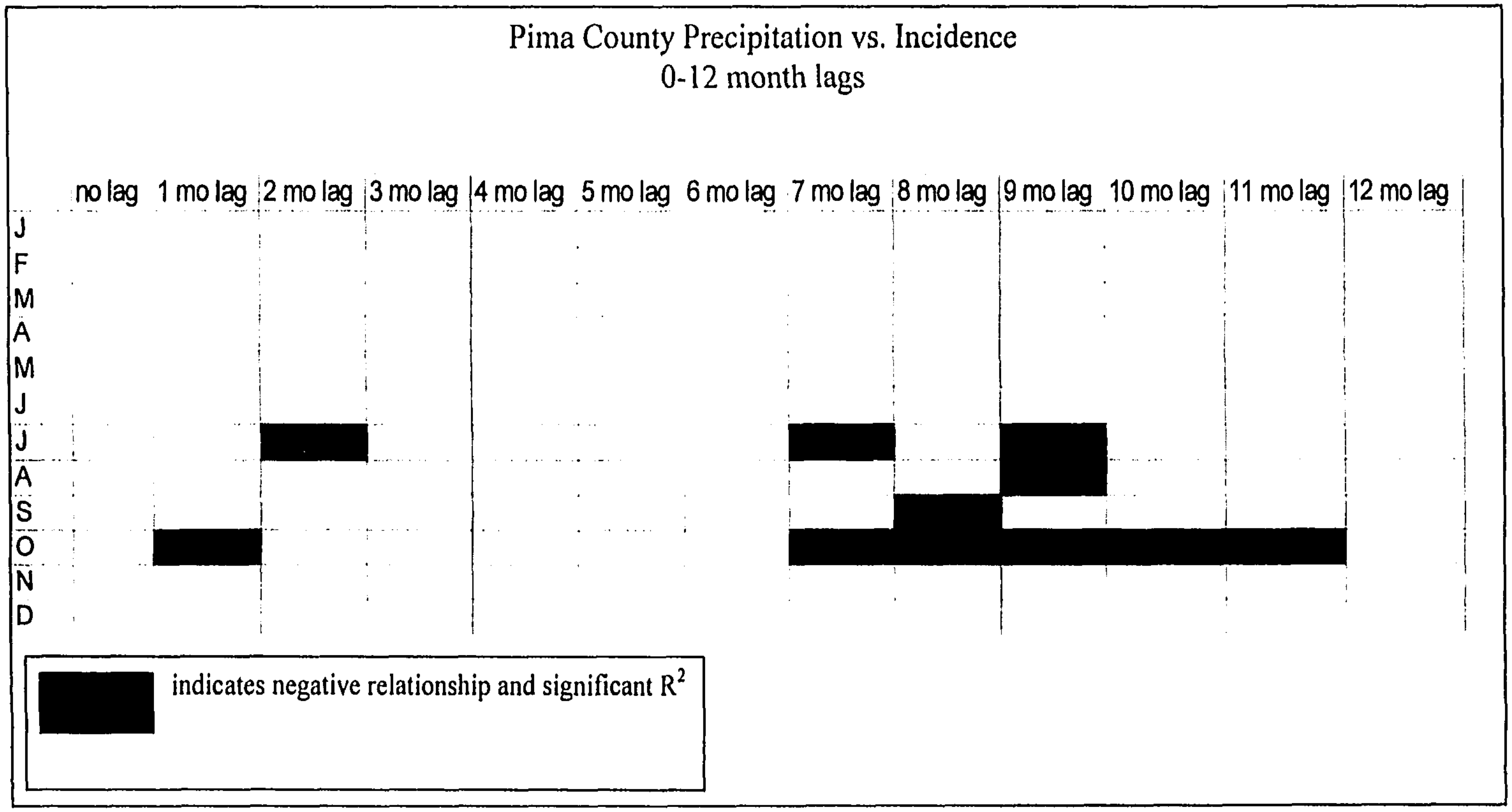

Fig. 3.6. Summer and early fall precipitation is negatively correlated with incidence in Pima County at varying lags.

one year. This long-term relationship is explored using composite analyses.

3.4.1.2 Air Temperature

Average air temperatures in July and August are positively associated with incidence in Pima County in the seven months that follow (Fig. 3.7). September temperatures are positively associated with incidence mainly only in shorter time periods, during the October and November that follow. Incidence in other months appears to be affected much less by average temperature. Minimum air temperature in July and August is positively associated with incidence in the months that follow, particularly early fall and winter. Higher than normal minimum temperatures during the summer likely correspond to increased humidity related to the monsoon circulation. Maximum temperatures in July, August, and September appear to positively affect incidence in the short term, in the one or two months that follow. Higher than normal maximum temperatures in summer may lead to below normal soil moisture provided by monsoon storms, thereby allowing the fungus to become airborne and infections to occur in the next few months. Shorter term wet and dry cycles, on the

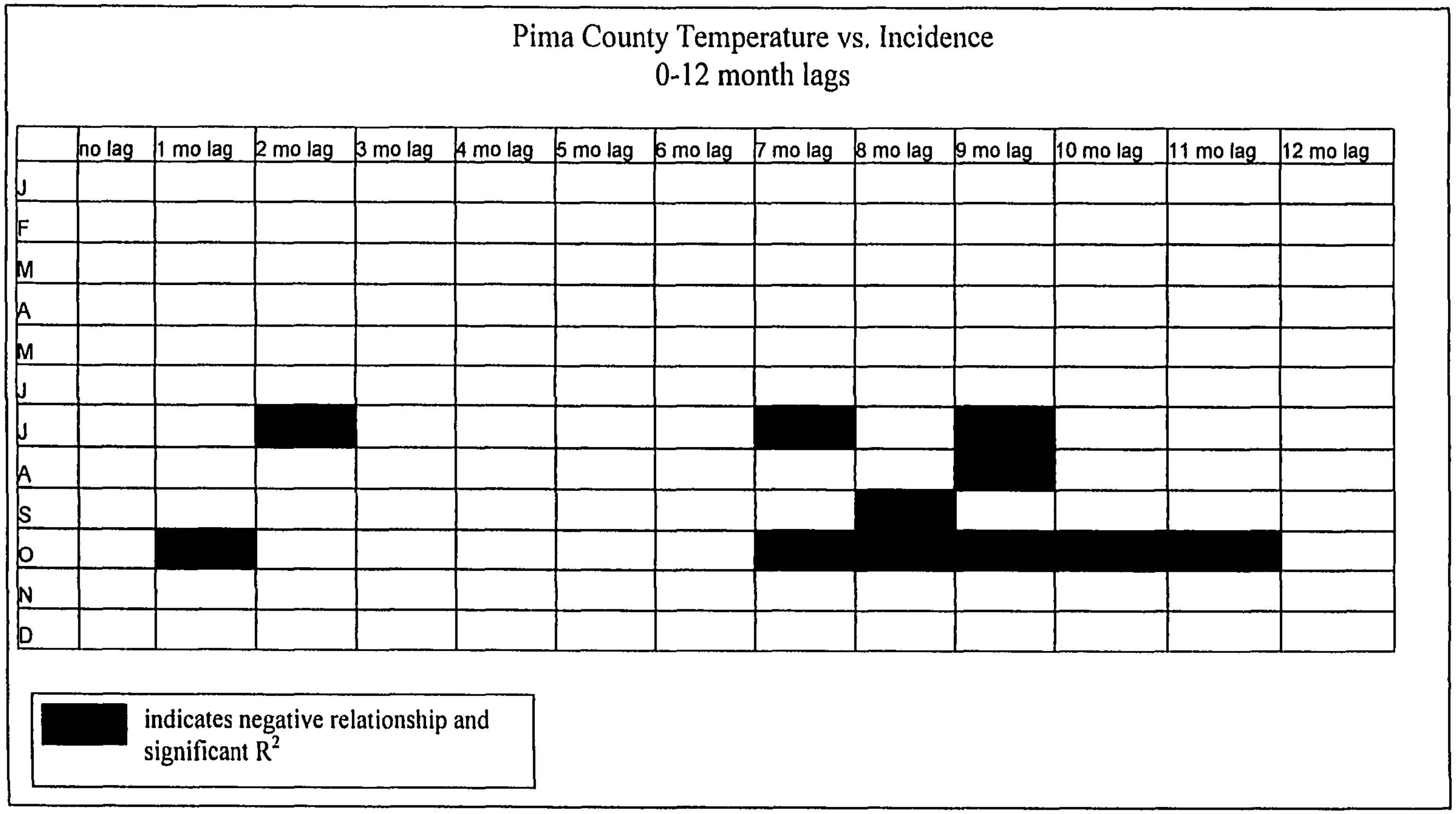

Fig. 3.7. Temperatures in summer and early fall are negatively correlated with valley fever incidence.

order of days or weeks, may more heavily impact fungal growth than monthly cycles, however without fungal counts from the soil or air, this relationship is very difficult to examine. This finding also fits well with previous research that associates high temperatures with soil sterilization. Given the results of our correlation analysis, it appears that extreme summer temperatures in particular are important. Higher than normal summer temperatures may selectively kill other microorganisms in the soil, and when moisture returns to the soil *C. immitis* may be able to reproduce relatively free of competition leading to increased incidence in the months that follow (Maddy 1957). Whatever the mechanism, higher than normal summer temperatures lead to higher than normal incidence in the future.

3.4.1.3 Dew Point Temperature

Average dew point temperature in the first seven months of the year are significantly associated with incidence in only one or two months with few clear, consistent patterns. It was expected that dew point temperature, as an indicator of moisture content in the air, would affect the ability of the fungus to become airborne; high moisture content in the air would translate to somewhat moist top soil. However, the few possibly spurious high correlations did not indicate an association between dew point temperature and incidence.

3.4.1.4 Wind Speed

Daily wind speed data were averaged by month to match the monthly incidence data. At this temporal scale, a relationship between wind speed and incidence is not significant. It is more likely that individual, daily wind events, such as very high gusts, affect incidence rates of valley fever. Gust data and maximum sustained wind speed were not analyzed in this study, however they would be an important part of future analyses.

3.4.1.5 Palmer Drought Severity Index

The PDSI value has a lagged negative influence on incidence in every month in which there is an apparent relationship. PDSI in the latter half of the year has a much stronger influence on incidence in the months that follow than in the early part of the year. The PDSI value in September is correlated with incidence in the remainder of fall, winter, and the next spring. October PDSI is correlated with incidence in the months that follow, through the end of summer. The PDSI value in November is associated with incidence in January and May, as well as the following fall. In the short term, PDSI is likely negatively correlated with incidence because soil moisture prevents the fungus from becoming airborne. Conversely, if PDSI values are near zero or negative, the soil is likely to be dry and more infections may occur.

3.4.2 Composite Relationships

3.4.2.1 PDSI Composite

PDSI does not fluctuate rapidly, but rather is smoothed over time. This is apparent in most composites, in that PDSI does not fluctuate greatly over the four-year time period. The autocorrelation inherent to the index creates smoothly changing values rather than high fluctuations around the mean. Most monthly composites indicate that a month with high (low) incidence is preceded by drier (wetter) than average conditions, as indicated by PDSI. During some months, such as November (Fig. 3.8), PDSI values fall below the mean for the entire forty-eight month composite. Other months, including January (Fig.

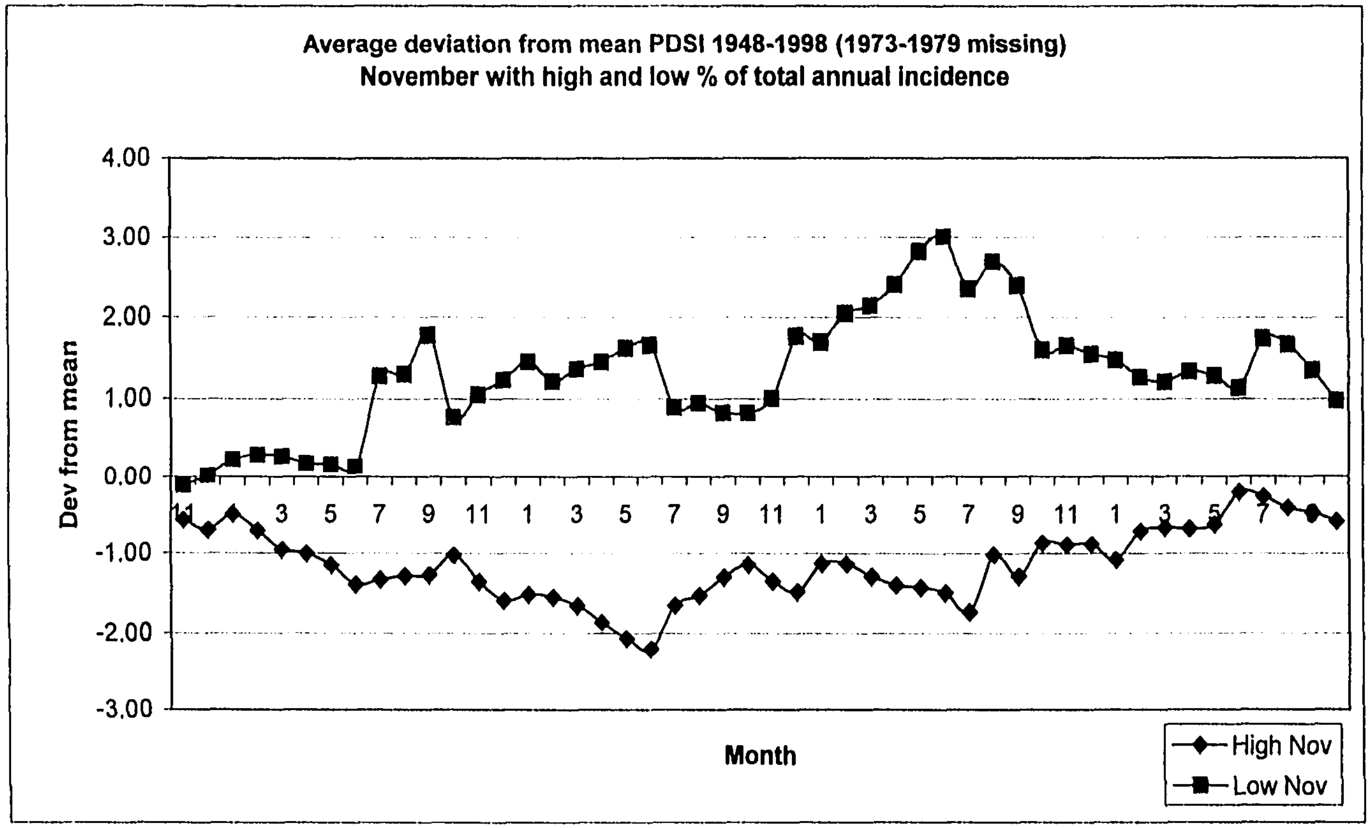

Fig. 3.8. PDSI values fluctuate very little prior to November with either a high or a low percentage of total annual incidence.

3.9), show PDSI values that fluctuate around the mean. A marked dry period is found about six months prior to a month with higher than average incidence. This dry period may allow the fungus to break apart within the soil and more easily be dispersed. The June through September time period with above average incidence is preceded by above average PDSI values for almost the entire forty-eight month composite. This pattern was not expected, but perhaps indicates that the fungus responds to shorter timescales than PDSI, which is highly smoothed over time.

April, May, and October with a high percentage of annual incidence show an interesting moisture pattern that fits well with past findings. In the composite graph for all three months (Fig. 3.10), above average moisture conditions are apparent about two to three years prior to a month with high incidence, according to PDSI values. During this time of above average moisture, the number of fungal spores was likely increasing within the soil. A drying trend occurs following that time period, during which the fungus can break apart and become airborne. A reverse pattern exists during some months with a low percentage of annual incidence. Two to three years prior

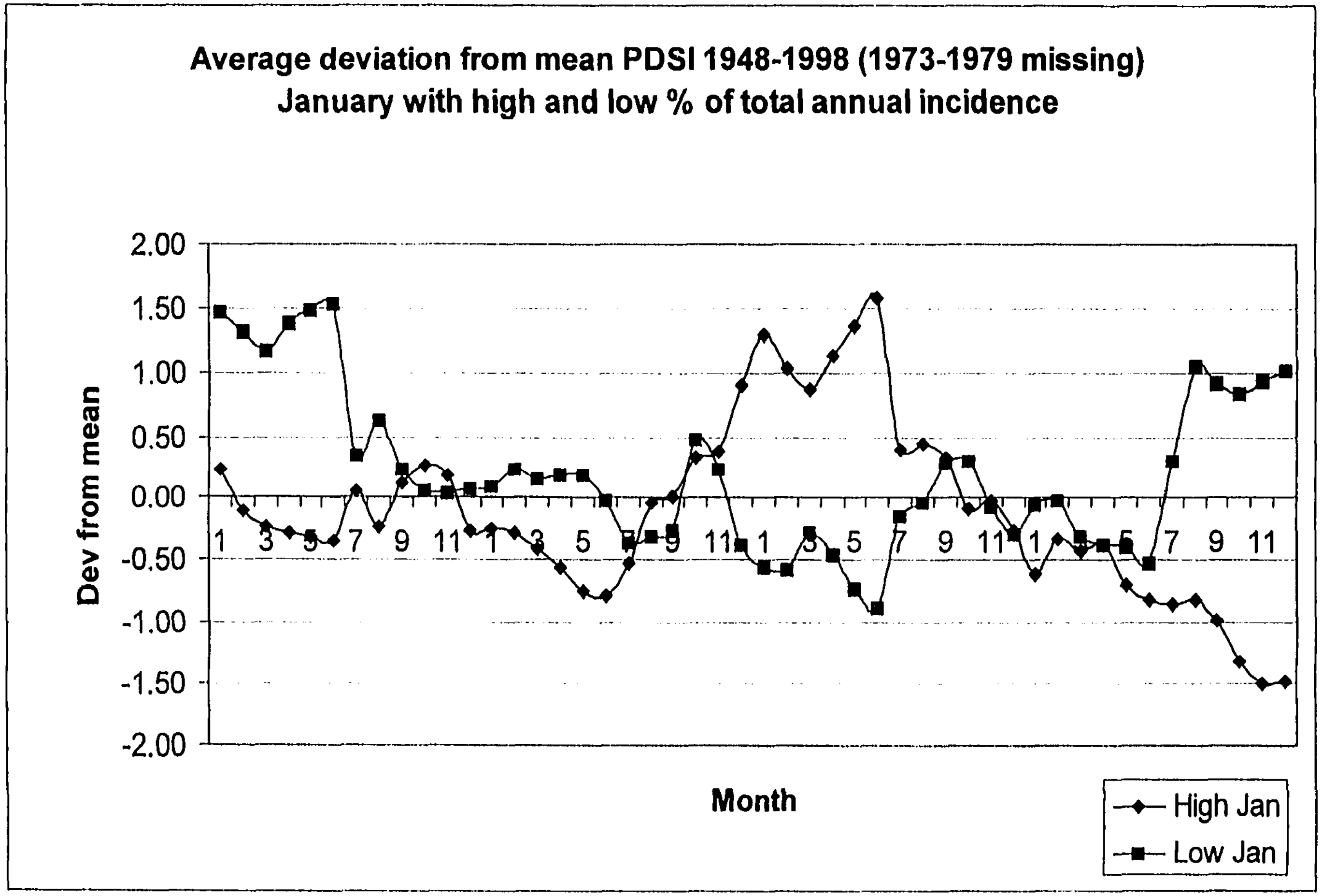

Fig. 3.9. PDSI values are highly varied prior to January with a high and a low percentage of total annual incidence.

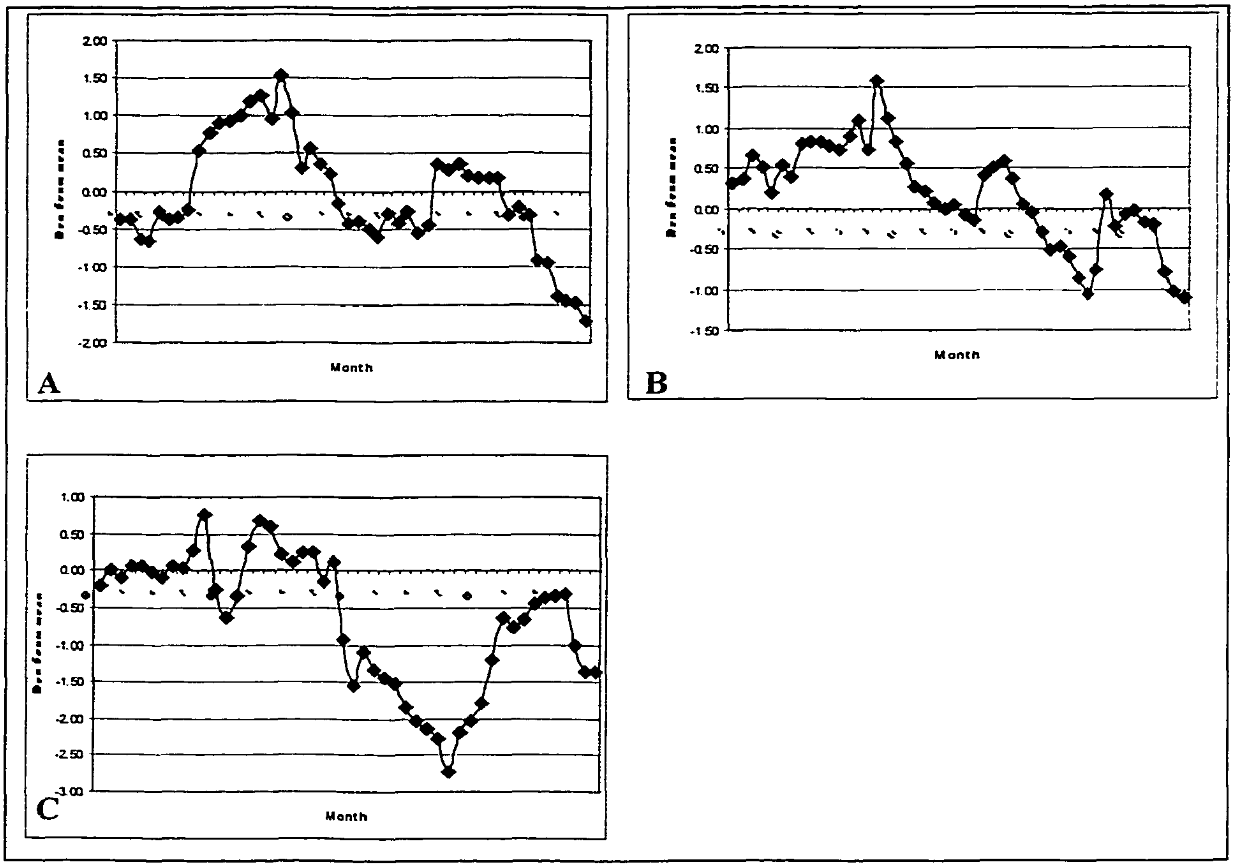

Fig. 3.10. PDSI composites for April (A), May (B), and October (C) with a high percentage of total annual incidence show a similar pattern of moist and dry conditions.

to a month with a low percentage of annual incidence, conditions appear to be drier than average. Low moisture diminishes fungal growth, and therefore during dry periods, the fungus may survive in the soil without producing arthroconidia. A trend of increased moisture follows, which may prevent the fungal spores that survived from becoming airborne.

3.4.2.2 Precipitation Composite

The composite graphs for precipitation show patterns similar to PDSI. Months with a high (low) percentage of annual incidence are often immediately preceded by lower (higher) than average precipitation. During the summer, (June through September), months with a high (low) percentage of total annual incidence are characterized by higher (lower) than average precipitation for much of the previous twelve through thirty-six months. Although deviation from mean precipitation is highly varied prior to a month with a high percentage of monthly incidence, in most graphs a pattern appears twenty-four months prior that indicates above average precipitation. This again points to the need for moisture to allow the fungus to grow abundantly.

The January graph (Fig. 3.11) provides an example of the complexity of the composite analysis for precipitation. Some expected patterns are visible. Two years prior to a January with a high percentage of total annual incidence, above average precipitation is received, while a drying trend is present in the months immediately prior to the high January.

3.4.2.3 Temperature Composite

The temperature composite graphs are also highly varied, but some patterns are apparent. Months with a high percentage of total annual incidence are often preceded by higher than average temperatures. This factor is likely related to soil moisture, as well as the soil sterilization hypothesis involving summer temperatures. High temperatures increase evaporation, leaving the soil dry and the fungus able to become airborne. Some months with a low percentage of total annual incidence are preceded by lower than average temperatures, however the pattern is not as consistent as that of high incidence months. Approximately two years prior to a month with high incidence, the composite graphs for some months show below average temperatures. This decrease in temperature coincides with

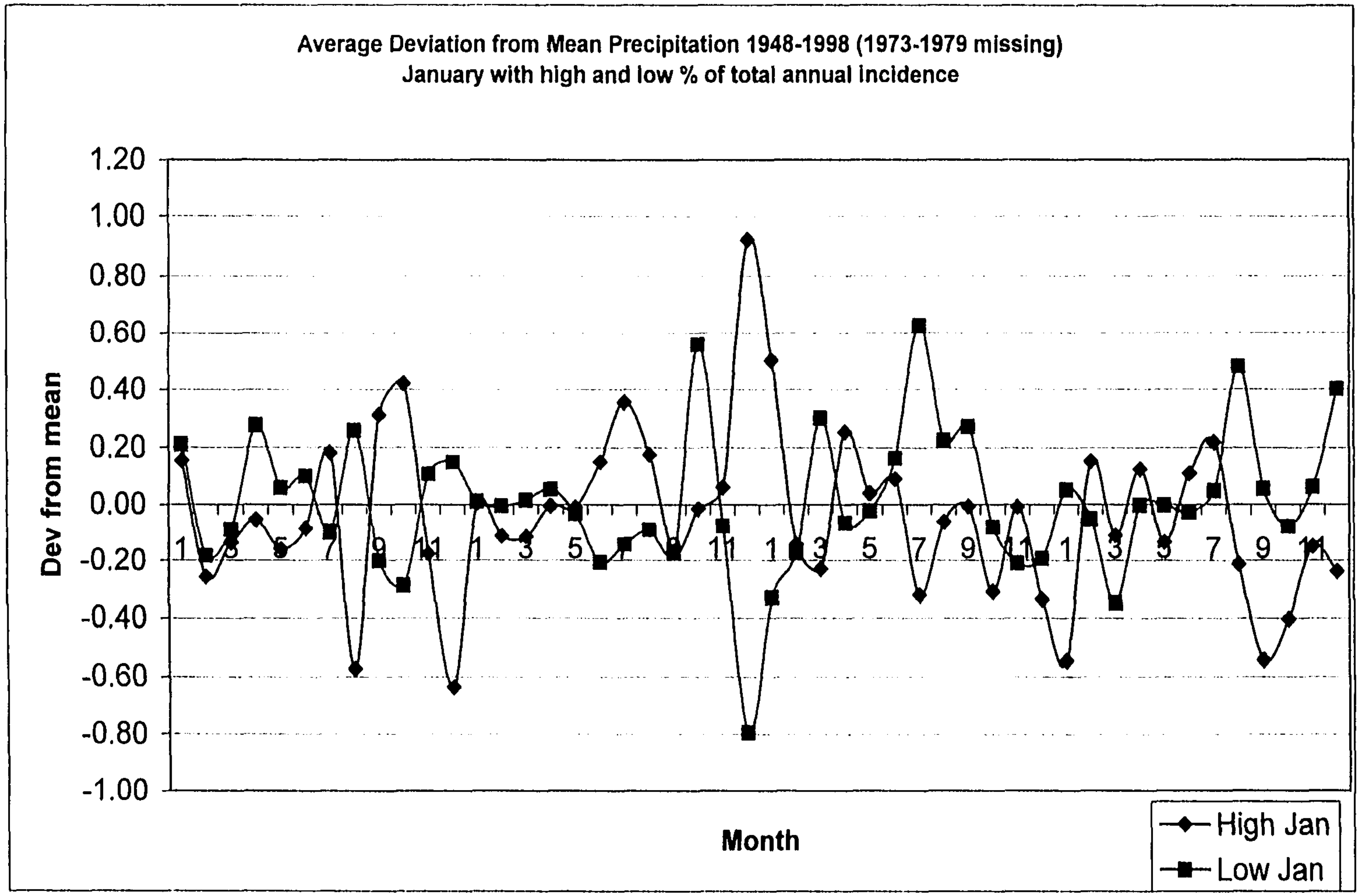

Fig. 3.11. The precipitation composite leading up to a January with high and low percentage of total annual incidence is complex and highly varied.

the period of increased precipitation that allows the fungus to grow in higher than average numbers.

The composite graph for January (Fig. 3.12) with a high percentage of total incidence illustrates the above points. Temperatures in October are above average, and along with below average precipitation, soil moisture conditions likely allow fungal spores to become airborne more easily. November and December approximately two years prior to a January with high incidence experience below average temperatures and receive above average precipitation. These conditions in the soil may foster an environment conducive to the growth of the fungus. Therefore, more fungal spores may be available when conditions are right for the fungus to become airborne, resulting in higher than normal incidence.

3.4.3 Model Development and Variables

Variables shown to be useful in predicting valley fever from the exploratory data analysis were included in the model development. The monthly models were designed to predict deviation from mean percent of the total annual incidence, using deviation from mean climate conditions for varying time periods as variables. It was determined that

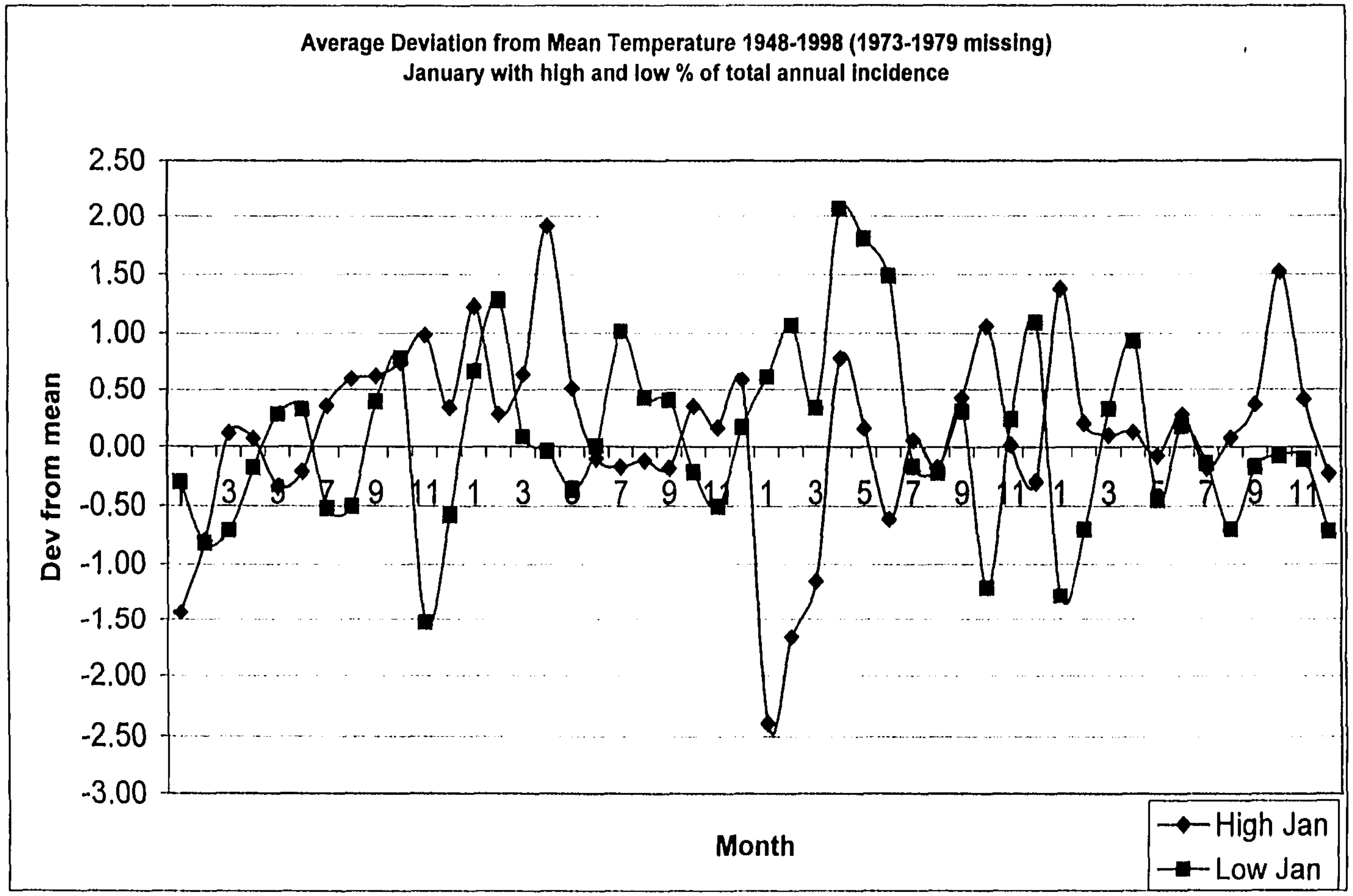

Fig. 3.12. The temperature composite for January is also highly varied and complex.

given uncertainties about the quality of the incidence data, it would be difficult to accurately predict the precise number of cases. Rather, the models were designed to predict monthly incidence as relatively above or below average (as defined in the methodology section). The entire data record, 1948-1998 (1973-1979 unavailable), was used in the model development.

Potential variables included temperature and precipitation for a time period of up to four years prior to the month being predicted. PDSI variables were not included in the model development. PDSI values are not forecast into the future, and since the goal of modeling in part is to use forecast climate conditions, PDSI was deemed to be less useful to actual model development. The variables included in model development also incorporated a number of interaction terms that were developed for each month. Precipitation and temperature for important time periods were multiplied to allow for complex relationships.

Eleven to fourteen variables for each month were selected for model development. Some of those variables were highly correlated with one another (e.g., interaction term of temperature and precipitation, and the precipitation variable for the same time period), therefore a principal components analysis was conducted for each month in order to avoid multicollinearity and increase parsimony. The original variables were reduced to five to eight components. The highest loading variable in each component, as well as those variables that were not highly loading in any component but were logical to include, were entered into the modeling procedure.

The monthly models were initially developed on all data using a backward stepwise regression procedure to reduce the variables to those that were statistically significant. The relatively small number of years (n=44) for model building made standard cross-validation techniques, in which a subset of the data are set aside for testing, difficult to use. Therefore, a jack-knife (leave-one-out) cross-validation technique was employed. After a monthly model was developed on all data using the backward stepwise procedure, the selected variables were forced into individual non-stepwise models in which data for one year was left out. This process was repeated so that each year was left out of the process one time. Each instance of the model then attempted to predict the year that was left. This resulted in n=44 independent data points.

The variables chosen for each model are outlined in Table 3.1, along with the t-statistics and significance for each variable. Most of the variables selected by the modeling procedure are from time periods of one year or greater from the month being predicted. It appears that short-term climate conditions are not as important in predicting incidence as long-term conditions. This is partly counter-intuitive, but may be a result of shorter-term processes being filtered out in the many steps between fungal growth and severe disease incidence. About 40% of the variables chosen are either winter temperature or winter precipitation of varying time periods. It therefore appears that conditions during winter have more of an effect on incidence during any month than conditions during other seasons, and are therefore more useful in prediction. Winter precipitation is more consistent than summer thunderstorms, and is characterized by soaking rains rather than intense storms, and perhaps moisture that soaks into the ground is more important to *C. immitis'* lifecycle than summer rainfall that often flows over the surface without soaking into the soil. Data for winter precipitation appear to be more reliable for use in the models. Winter temperatures may indicate that the fungus is not able to

Table 3.1. Variables and coefficients for each monthly model.

	Coefficients	t-stats	Significance
January			
(Constant)	-0.787	-1.868	0.070
D-Jan 1 Yr P	-0.428	-2.093	0.043
O 1 Y T	0.374	2.102	0.042
Dec 1 Y T	-0.415	-2.069	0.045
Apr-Jun 1.5 Y T	-0.176	-2.227	0.032
February			
(Constant)	3.13	38.19	0.00
S-Jan trend P	0.13	2.47	0.02
N-D 2 Y T	0.05	2.10	0.04
March			
(Constant)	5.87	4.71	0.00
N-D 1 Y P	-1.09	-2.96	0.01
F-Mar 2 Y P	1.86	5.47	0.00
Aug-Nov P	-0.56	-3.48	0.00
D-Mar 1 Y trend P	1.13	2.80	0.01
O-Jan 2.5 Y P	-0.35	-2.22	0.03
Jan 2 Y T	0.50	2.91	0.01
F-Mar 2 Y P*Mar-Jun 2 Y T	-0.03	-4.95	0.00
April			
(Constant)	3.093	35.111	0.000
D-Mar 2 Y P	-0.112	-2.932	0.006
S-Jan 2.5 Y trend P	0.165	2.420	0.020
Nov 2.5 Y T	-0.137	-3.512	0.001
D-Mar 3.5 Y T	-0.032	-2.098	0.042
May			
(Constant)	3.112	37.431	0.000
Feb-Apr P	-0.177	-2.691	0.010
Aug-Dec .5 P	-0.072	-2.222	0.032
Nov-Jan 1.5 Y T	0.041	1.972	0.056
Sep-Oct 1.5 T	-0.053	-1.912	0.063
June			
(Constant)	10.3084	114.30	0.00
Sep-Dec .5 Y P	0.0330	3.83	0.00
Apr-Aug 3 Y trend P	0.0677	3.60	0.00
Sep-Dec .5 Y P*Jul-Oct .5 Y T	-0.0008	-3.43	0.00

Table 3.1. (cont.) Variables and coefficients for each monthly model.

	Coefficients	t-stats	Significance
July			
(Constant)	3.862	1.909	0.064
Jul-Dec 2 Y P	0.631	4.009	0.000
Nov-Mar 1.5 Y T	0.200	3.001	0.005
Apr 3.5 Y T	-0.364	-2.170	0.037
Nov-Mar .5 Y P	0.357	2.029	0.050
Jun P*Jun T	-0.044	-2.242	0.031
DEC .5 T	0.383	1.770	0.085
August			
(Constant)	-5.599	-2.747	0.009
JAN P	0.877	1.759	0.087
Sep 1 Y P	1.598	3.020	0.005
JUL T	0.812	2.178	0.036
Jul-Sep 1 Y T	-0.548	-4.254	0.000
Oct-Jan 1.5 Y T	0.188	1.784	0.083
Apr 2.5 Y P*Apr-Jun 2.5 Y T	0.027	2.806	0.008
September			
(Constant)	2.969	108.799	0.000
Jul-Nov 1 Y T	-0.015	-2.827	0.007
Dec-Feb .5 Y P	0.032	2.630	0.012
Aug-Oct 3 Y P	0.029	2.016	0.051
October			
(Constant)	98.70	16.70	0.00
May-Sep T	6.13	5.27	0.00
Mar-May 2.5 Y P	-24.80	-4.17	0.00
Mar-May .5 Y P	-11.99	-2.11	0.04
November			
(Constant)	-12.393	-2.753	0.009
SepP*Sep-OctT	0.031	2.706	0.010
Feb-Jun 2.5 Y T	0.229	2.444	0.019
Jun-Sep 3.5 trend T	-0.671	-2.857	0.007
Jan 1.5 Y T	-0.781	-2.963	0.005
December			
(Constant)	2.174	26.613	0.000
May 1.5 Y T	-0.114	-3.338	0.002
Dec 1 Y T	0.105	2.724	0.010
JUL T	-0.151	-2.447	0.019

survive at temperatures below a certain threshold. Given the improved ability to forecast winter climate in the Southwest, the models should be better able to forecast incidence than if more summer climate variables were included. It was expected that the interaction terms would be useful predictors given the importance of soil moisture, however only four were chosen during the regression procedure.

3.4.3.1 Model Evaluation

The models were evaluated using the independent data set aside as part of the jack-knifing process when the models were developed. The coefficient of determination (explained variance) ranges from low to moderate values (Fig. 3.13). In all cases, the F-statistic associated with the model was significant (α=0.05). The best model results in terms of explained variance were found in models for months that have the highest percentage of total annual incidence, as indicated in Figure 3.13. Fortunately, we are better able to predict incidence in the months that are of the highest concern. Root mean squared error (RMSE) was calculated for each model (Table 3.2), and ranges from 27%

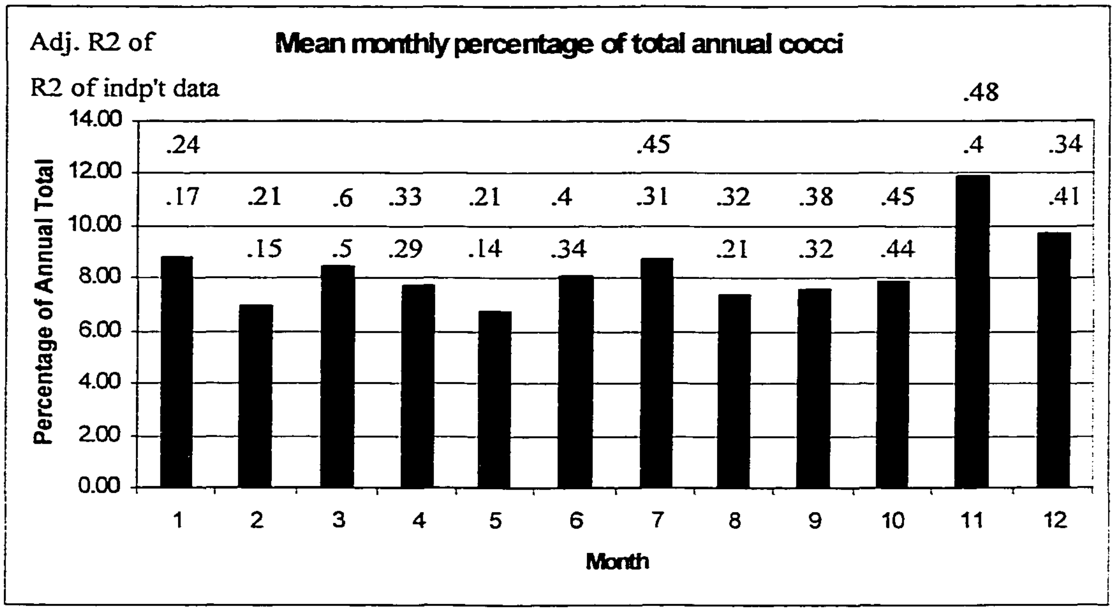

Fig. 3.13. R^2 values range from low in May to high in March. Months with the highest percentage of annual incidence (November and December) have moderately high R^2 values.

Table 3.2. RMSE percentages of average deviation from mean incidence are moderate for months with a high percentage of annual incidence.

	Model R^2 (Adj. R^2)	Independent R^2	RMSE %
Jan	.315 ([illegible])	.17	32
Feb	.257 (.207)	.15	44
Mar	[illegible]	[illegible]	[illegible]
Apr	.396 (.334)	.29	47
May	.252 ([illegible])	[illegible]	50
Jun	.443 (.401)	.34	34
Jul	[illegible]	.31	37
Aug	.417 (.323)	.21	42
Sep	[illegible]	.32	52
Oct	.490 (.451)	.44	27
Nov	.526 (.477)	.40	38
Dec	.385 (.339)	.41	40

to 50% of the average deviation from percent of total annual incidence in the observed data. Although RMSE values are high, those months with the highest percentage of total annual incidence have lower RMSE values than months with low percentage. The models are able to predict independent points fairly well, however they fail to capture extremes in many cases. Figure 3.14 illustrates the ability for the November model to predict observed values.

Residuals were examined in an attempt to explain the portion of the variance unaccounted for by the model variables. No clear consistent pattern is apparent in the residuals that can be explained by a variable that was not included. However, it is likely that a portion of the unexplained variance in incidence is due to climatic events that occur on a smaller time scale. Individual wind and dust events occurring on a daily or weekly basis affect incidence, however they are not captured in the model due to the use of monthly climate data. Also, soil moisture is likely an important factor in the lifecycle and dispersal of *C. immitis*, and although PDSI was used as a proxy for soil moisture, a more exact measure of soil moisture would improve the model. Finally, the models could be improved

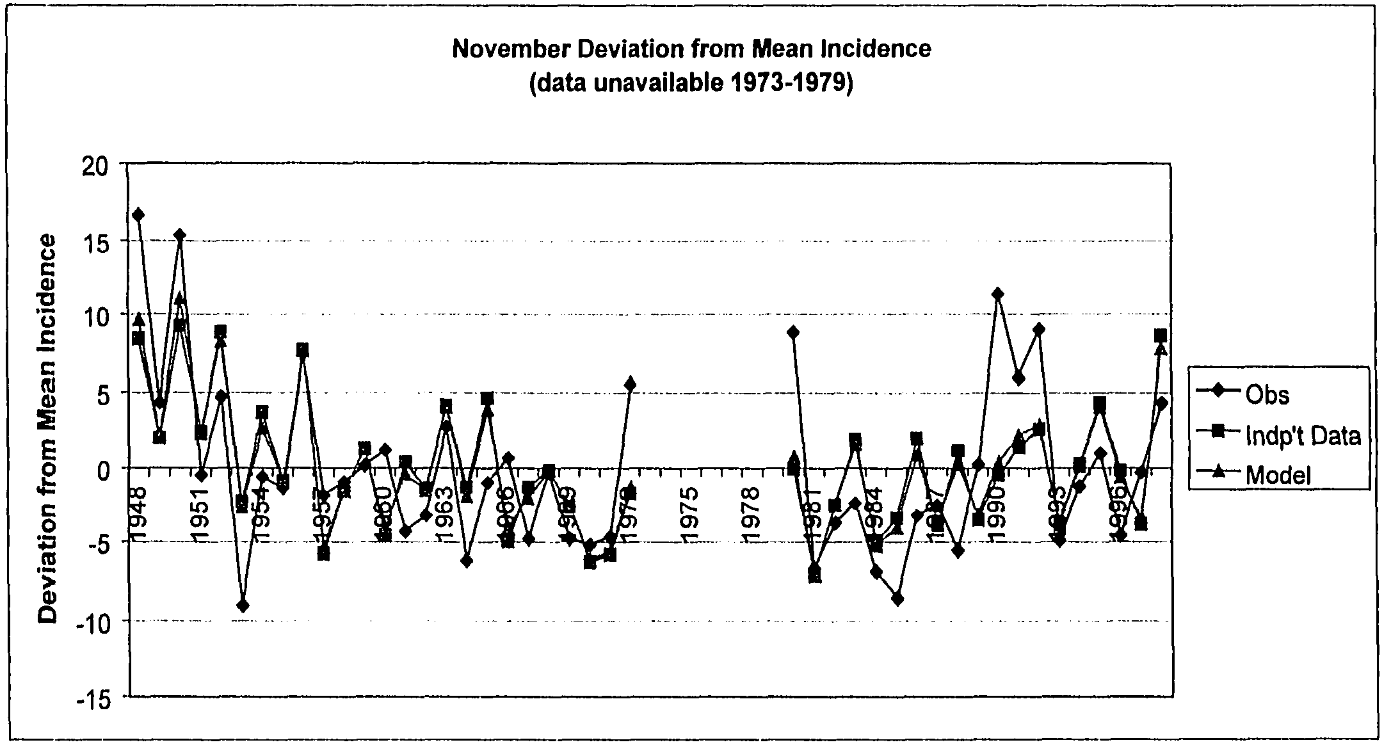

Fig. 3.14. The November model is able to predict the variation in incidence, however it fails to capture extreme values in many cases.

through the incorporation of spatial variables including soil type, disturbance regime, and proximity to riparian zone.

3.5 Summary and Conclusions

The first portion of this study consisted of an exploratory data analysis that sought to understand the basic relationships between climate conditions and incidence. The bivariate and composite analyses provided insight into the conditions up to four years prior to a month with high or low incidence. This process also aided in the selection of variables for inclusion in the development of the multivariate model. Predictive models were developed using a backward stepwise regression, and incorporated temperature and precipitation variables at varying time periods prior to the month being predicted. The resulting models included variables that were mainly from time periods of greater than one year prior to the month being predicted. Also, winter climate conditions appear to be important incidence predictors, as winter temperature and precipitation variables frequently appear in the models. Months with the highest percentage of total annual incidence have the best performing models, according to R^2 and RMSE. Therefore, we are best able to predict incidence in the months that experience the greatest number of cases.

Several hypotheses of the research were supported by our findings, while evidence was not apparent for other premises. The hypothesis regarding soil moisture conditions was supported by the results of the composite analysis. Moisture is required to the fungus to grow in large amounts within the soil, but a dry period is required for airborne dispersal. This pattern was found in the composite graphs for months experiencing above average incidence. Also, the soil sterilization hypothesis was supported by findings in the bivariate analysis. The positive relationship between incidence and summer temperatures indicates that high temperatures may lead to a high number of cases. During the study, other interesting relationships were found that had not previously been documented. These may be real, or may be related to the nature of the data and analyses. They are statistically significant, however, and should be investigated further. The importance of winter precipitation and temperature variables in the models that were developed point to the winter season as having more of an impact on incidence than other seasons. This result was unexpected given previous studies and the exploratory analysis. In future studies, more attention should be given to the role of winter climate in predicting incidence.

Valley fever incidence is increasing within the endemic zone in Arizona as the general population grows, as well as in the population of susceptible groups. Previous research links valley fever incidence with climate conditions. This study adds to that literature by improving the understanding of this complex relationship, and by developing a predictive model. We are working with state health officials as well as researchers within the Valley Fever Center for Excellence to implement the monthly models as a guide to the likelihood of above or below average incidence in future months. Pima County is currently experiencing an upward trend in cases, and model results can be integrated in an attempt to partially explain this increase. Given past, current or forecast temperature and precipitation conditions, the user can determine if incidence will be high in future months. The information can be passed along to health care providers who can prepare for increased cases by ensuring that the proper treatment is available. Also, doctors in other regions may recommend that susceptible people not travel to or through the endemic zone if conditions are right for increased cases. Model runs using forecast climate conditions are sensitive to the quality of those forecasts, which must be considered by the user. Improved, better informed models could be created if fungal count data become available in the future. Also, an analysis of wind gust data and a measure of soil moisture would be very useful to further understand the relationship between climate conditions and valley fever incidence.

Chapter 4 - Conclusions

Climate and valley fever research fits into a larger climate and health agenda that seeks to understand the impacts of climate variability and change. The relationships between climate and valley fever incidence revealed in this project add to the overall understanding of the disease, and could be expanded to explore the impacts of climate change on incidence rates and the range of the disease. The study borrows from traditions in medical geography that aim to understand relationships between disease, society, and the environment, and seek to promote adaptation to a disease. The analyses and predictive models from this study have improved understanding of the disease, and have provided an opportunity for society to respond to potential increases in incidence.

The research was conducted at the intersection of a university-wide, interdisciplinary group examining valley fever and an assemblage of scientists studying the impacts of climate variability. Researchers associated with the Valley Fever Center for Excellence are studying a wide variety of aspects dealing with the disease, including isolation of *C. immitis* in the soil, the analysis of canine incidence data, and a range of medical studies including the development of a vaccine. The results of this study will add to the overall development of knowledge by providing an improved understanding of climate relationships. Since a vaccine is unlikely to be developed for five to ten years, the predictive models from this study will be useful for raising awareness among health care providers, state health officials, and the general public as to the likelihood of high incidence. The study was also based within and supported by the Climate Assessment of the Southwest Project that aims to understand the impacts of climate variability upon humans. Human health is an important part of climate variability research, and the model developed in this study can be used in concert with climate forecast models and fine-scale spatial climate data developed by others in this research group.

Populations particularly susceptible to the disseminated form of the disease are growing in number in Pima County. The area is popular for elderly winter residents, and the number of people with suppressed immune systems is also increasing within the county. Tourism attracts people from other regions and countries that have not previously been exposed to the disease, and who may return home infected with the fungus and become ill. Therefore, a national and international awareness of the disease is important. The monthly multivariate models will provide some insight into the level of incidence in future months, and a warning system can be implemented in which the user, possibly at the Valley Fever Center for Excellence (VFCE), inputs climate data into the model and distributes the results that could be useful to doctors. The VFCE website would be a useful location for posting forecast information. The implementation of a model is not without its caveats however. Tourism and in-migration may be negatively affected if a prediction of particularly high incidence is made. The model should be applied with caution, however its usefulness in preventing serious cases of valley fever should not be overlooked.

In limiting the study to examining the relationship between incidence and climate conditions, and the development of a predictive model, certain aspects regarding valley fever were not addressed. Environmental factors work in unison with social factors to cause the disease. For example, construction activity could potentially aid spores in becoming airborne and the annual cycle of migration of winter residents could both affect the incidence time series. Factors such as the aforementioned were not included in order to isolate the effects of climate. Qualitative analyses that may look at the particular individuals becoming sick or the access to health care for those infected were also not addressed in this study. The research concentrated on environmental factors, but future work could expand to include social issues related to valley fever incidence.

Much research remains in analyzing detailed aspects of valley fever incidence. With data available in the future that provides counts of *C. immitis* spores in the soil, the relationships between climate and incidence uncovered in this study could be improved and clarified. The models developed in this research predict deviation above or below the mean. With count data, a more precise prediction of incidence could be made. Also, future research could address social aspects of the disease, including analyses of at-risk groups and access to treatment.

APPENDIX: GLOSSARY OF TERMS

Arthroconidia - a spore released through the fragmentation of hyphae

Dimorphic - a species that has two distinct forms

Endospore - thick-walled, dehydrated structures that can resist extreme dryness and very high temperatures for long periods of time

Hyphae - long, thread-like strands of fungal cells, forming filamentous tubes

Mycelium - an interconnected mass of hyphal strands

Saprophyte - an organism that feeds on dead or decaying vegetable or animal material

Spherule - the form taken by the fungus within tissue during the parasitic phase of its lifecycle; multicellular structure

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