

Review Article

Environmental variability and coccidioidomycosis (valley fever)

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Abstract

Coccidioidomycosis (valley fever) is a disease endemic to arid regions in the western hemisphere, and is caused by the soil-dwelling fungus *Coccidioides immitis* (*C. immitis*). In this paper, we provide an overview of the current state of knowledge regarding valley fever and *C. immitis* as related to climatic conditions and habitat requirements. Previous research shows there is a relationship between temperature and precipitation, and outbreaks of coccidioidomycosis. Incidence of the disease varies seasonally as well as annually due to changing climatic conditions. However, the specific environmental conditions that may produce an outbreak of coccidioidomycosis are not well understood in space and time. Previous studies have attempted characterize *C. immitis*' habitat. Temperature, moisture, salinity, and pH of the soil have all been considered separately in the geographic distribution of the fungus. Medical and proactive intervention are served best, however, by an integrative strategy that folds climate and surface variables into spatially-explicit models. We conclude with recommendations for future research directions.

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 (Figure 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).

This paper reviews previous research that has discussed both the relationship between valley fever and climate, and the spatial variability of the disease including the soil properties required for the growth of

the fungus. The environmental aspects of the disease are the specific focus, rather than medical aspects. Although a body of research exists on the environmental aspects of valley fever, it has not been reviewed before. Introductory information on *C. immitis* and valley fever is followed by an overview of the existing state of knowledge regarding climate and the disease. An examination of previous research into the fungus' variability in the soil follows. We conclude with recommendations for future research that will lead to an improved understanding of both the relationship between climate and valley fever, and the habitat of *C. immitis*.

1.1 Lifecycle of *Coccidioides immitis*

C. immitis exists in both saprophytic and parasitic phases (Figure 2). The saprophytic or mold phase is one of the more hardy living structures in the biolo-



Figure 1. Areas of the United States and northern Mexico that are considered endemic for valley fever. (Adapted from Kirkland and Fierer 1996.)

gical world. It can grow in nature, under laboratory conditions, and in host tissues under particular circumstances (Fiese et al., 1955). The saprophytic phase of *C. immitis* is composed of entangled mycelia with immature hyphae 2 to 4 μm in diameter and septa at consistent intervals. Following about a week of growth, many of the hyphal cells mature into spores that are generally rectangular (arthrospores) or, occasionally, round to ovoid (chlamydospores) (Smith, 1972). The more common arthrospores alternate with smaller, sterile cells. These sterile cells breach easily, freeing the intervening arthrospores. In established communities, the entire mycelium may form arthrospores that detach easily within air currents. The arthrospores range from 1.5 to 4.5 μm in width and 5.0 to 30 μm in length (Huppert et al., 1967).

The parasitic phase was the first phase of the fungus observed by early investigators, and occurs

when a host inhales airborne arthrospores (Rixford and Gilchrist, 1896). In this phase, the fungus appears as a spherical, double-walled cell called a spherule, previously thought to be an ascus but now confirmed to be a sporangium. Spherules measure from 10 to 80 μm , and occasionally up to 200 μm (Schenken and Palik, 1942). A mature spherule typically contains a few to several hundred endospores 2 to 5 μm in diameter. The spherule eventually ruptures, discharging the endospores into the neighboring tissue. Each endospore is potentially capable of blooming into a new spherule. Immature spherules are more commonly detected in tissue than mature ones, and have clear cytoplasm without granules or endospores (Emmons, 1942; Baker et al., 1943).

Growth of the spherule phase of the fungus may be observed *in vitro* (MacNeal and Taylor, 1914) in a rich protein media when incubated around 37 °C. By con-

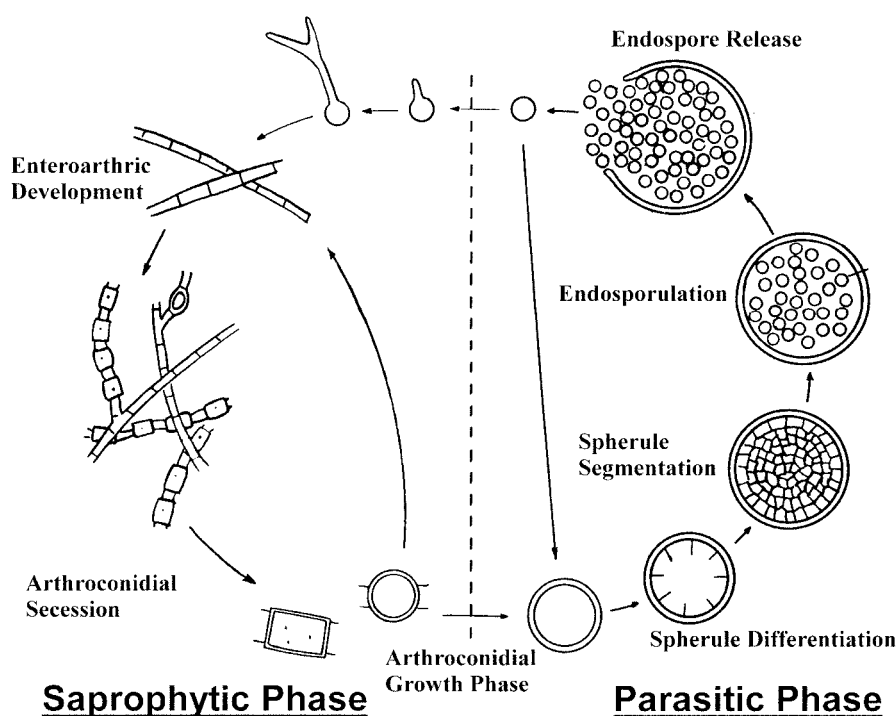


Figure 2. *C. immitis* exists in both saprophytic (left) and parasitic (right) phases. (Adapted from Fiese 1958.)

trast, *C. immitis* has been difficult to isolate in the soil. Cultures of the parasitic phase of *C. immitis* on media incubated at lower temperatures (25 °C to 30 °C) show germ tubes extending from the endospores or young spherules within 3 to 4 hours that later evolve into branching septate hyphae (Hampson, 1954). These spherules enter a host organism, where they multiply rapidly and induce the onset of valley fever.

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 and Barrett, 1996). The majority of the people infected (60%) either present no symptoms, or experience mild, cold-like conditions (Smith et al., 1946b). Some may endure a variety of flu-like symptoms which usually appear after an incubation 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 spherules enter the bloodstream and spread beyond the lungs (Einstein and Johnson, 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 and Johnson, 1992). Studies show cases of valley fever in people under the age of five and over the age of fifty are more likely to disseminate (Pappagianis, 1988). 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. Adult white females are less likely to have the disseminated disease than adult white males (Pappagianis, 1988).

Due to the migration of large numbers of people to areas of the southwestern United States where the disease is endemic, and because of the growing number of elderly people and persons carrying HIV, coccidioidomycosis is becoming an increasing health concern. In 1998 Arizona was the second fastest growing state in the nation. Today major population centers, Phoenix and Tucson, have grown in the same deserts of Arizona where *C. immitis* is most intensively endemic. In addition, the people who have populated these cities are primarily from non-endemic areas, thus it is unlikely they have previously been exposed to valley fever before migrating to the region. A comparable effect has also been seen in the endemic areas of California and west Texas (Galgiani, 1999).

As these populations have grown, an increasing proportion of persons unusually vulnerable to the most critical consequences of infection has risen commensurately. Significant increases in susceptibility to coccidioidal infections have often resulted from: antineoplastic chemotherapy, corticosteroid therapy, immune suppression for organ transplantation, and diseases that impair cellular immunity (Deresinski et al., 1974; Rutala et al., 1978). Coccidioidomycosis has frequently become an opportunistic infection due to the increasing application of organ transplantation (Cohen et al., 1982; Hall et al., 1993; Holt et al., 1997) and the spread of AIDS (Fish et al., 1990; Ampel et al., 1993; Jones et al., 1995; Singh et al., 1996). Suppression of cellular immunity permits reactivation of infections acquired years earlier, causing valley fever to be a problem beyond its endemic areas (Deresinski et al., 1974; Hernandez et al., 1987; Vartivarian et al., 1987; Holt et al., 1997). As an example, 46% of reported coccidioidal infections in patients with AIDS were described in persons outside the endemic areas of the southwestern United States (Jones et al., 1995).

Beyond the endemic areas, cases have been reported in visitors from numerous states (Harrell and Honeycutt, 1963; Nedwicki, 1963; Key and Smith, 1972) and from foreign countries; the Netherlands, France, Belgium, Germany, and Canada (Pappagianis, 1988). The resemblance of coccidioidomycosis to other diseases delayed its recognition and diagnosis. There is now, however, an awareness of the disease among physicians abroad.

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).

1.3 Geographic distribution of *Coccidioides immitis* and valley fever

With the exception of tropical areas in Mexico, most of the endemic regions are arid, with rainfall in the range of 12.5 to 50 cm, hot summers, few winter freezes, and highly alkaline soil. These factors match characteristics of the Lower Sonoran Life Zone (LSLZ) (Maddy, 1957). The LSLZ encompasses much of the area endemic for *C. immitis* and coccidioidomycosis, but spatial conformity is not precise (Lacy and Swatek, 1974).

Maddy noted that the south central portion of Arizona (Tucson and Phoenix) was the "...most infective area for mammals in the world known at present" and that statement remains true over forty years later, although cases occur in other areas of the state (Figure 3) (Maddy, 1958). In attempting to determine factors that favor the 'natural propagation of the fungus,' the author noted the following climatic characteristics in south central Arizona (Maddy, 1958): the mean July temperature in the shade is around 32 °C; the July mean maximum temperature is around 41 °C. The mean January temperature is around 10 °C; rarely does a freezing temperature occur at ground level for more than a few hours. Rainfall averages about 23 cm per year, and falls mostly in two seasons – summer and winter. The soil is mostly alkaline. The vegetation is quite typical of the LSLZ but is somewhat more abundant than in other areas of the Zone as the rainfall is above average. Based upon these climate and surface links, Maddy attempted to define areas in Arizona, California, Texas, New Mexico and Utah favorable to *C. immitis*' growth. However, these links have yet to be characterized at finer spatial scales.

2. Climate patterns

2.1 Background information on climate and *C. immitis*

There is documented evidence relating outbreaks of valley fever and climatic conditions. *C. immitis*

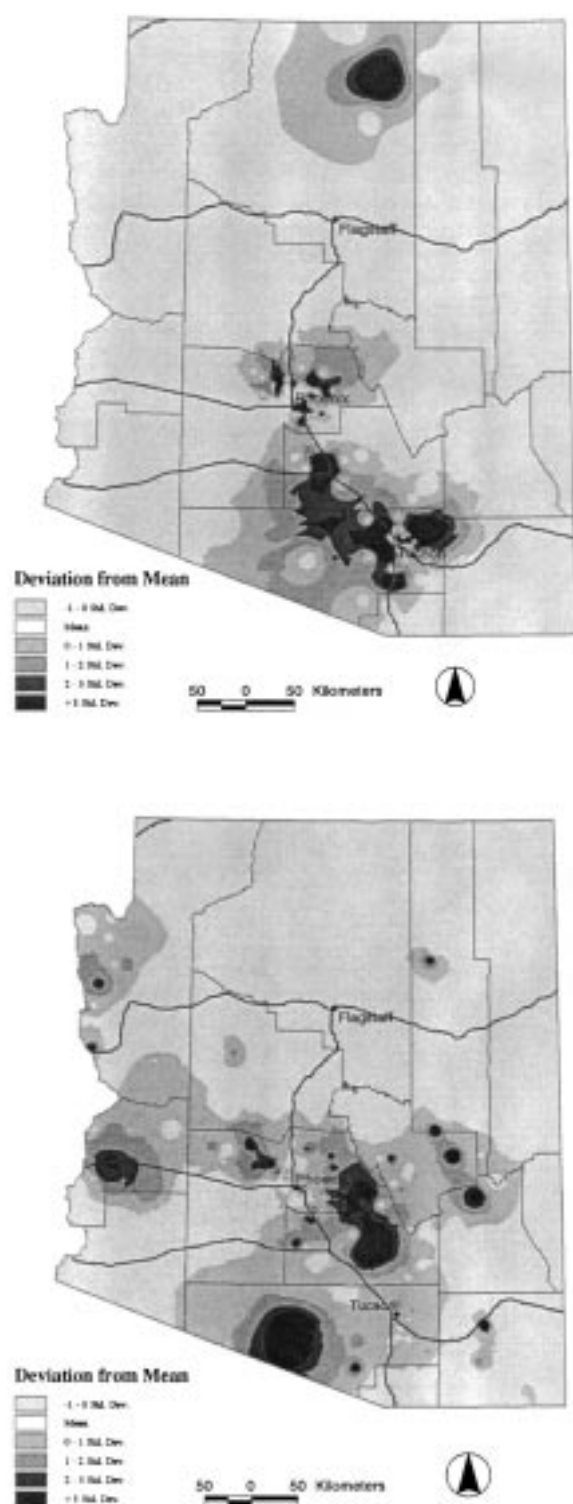


Figure 3. Spatial variability of valley fever incidence rates per 10,000 in Arizona in 1990 (top) and 1997 (bottom). (Source: Arizona Department of Health Services.)

is sensitive to climate variability, and responds to changes in moisture and temperature. Most prior work on valley fever was conducted decades ago, and focused mainly on the distribution of *C. immitis*, different phases of its lifecycle, and other aspects of valley fever. Only passing references are made in most studies 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 that shows a specific relationship between climatic conditions and incidence of valley fever.

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.

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 and Coccozza, 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 and Coccozza, 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 and Coccozza, 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).

2.2.1 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 et al., 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 et al., 1957).

Maddy 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 (Maddy, 1965). This study shows that *C. immitis* is most often recovered from the soil in the time period following the rainy season, and more rarely during the hot, dry season.

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 noted the majority of human infections seem to occur during the windy, dusty period following the wet season (Maddy, 1965). 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" (Hugenholtz, 1957).

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.

2.3 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).

2.3.1 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 and Swatek, 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 and Swatek, 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 and Swatek, 1957). Temperatures between 49 °C and 54.4 °C were often recorded during the time of the study (Plunkett and Swatek, 1957). It was noted that moisture was not evident in the soil at the 100–150 mm level during August, September, and October (Plunkett and Swatek, 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” (Maddy, 1965).

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 et al., 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.

2.4 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 and Einstein, 1978). Rain-fall several days after the dust storm prevented the epidemic from being any worse (Pappagianis and Einstein, 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 et al., 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 et al., 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 et al., 1946a). Other methods of dust control included paving roads and vegetating lawns and fields (Smith et al., 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 et al., 1946a).

3. Soil relations

3.1 Background information on soil and *C. immitis*

C. immitis was first isolated from soil in 1932 (Stewart, 1932), next to a bunkhouse at Delano, California. Filipino farm workers quartered at the bunkhouse developed coccidioidal granuloma, prompting a sampling of the soil. *C. immitis* is able to survive in the soil for lengthy, although not completely resolved periods of time. Even after burying infected 'canine, murine, or bovine tissues', the fungus could be found proliferating in soil near Phoenix, Arizona (Maddy et al., 1967). During these seven years, soil obtained around 64 meters away remained negative save one specimen (Maddy, 1965). Swatek et al. (1967) demonstrated survival of the organism for twelve years.

3.2 *Coccidioides immitis* and moist Soils

Heavy rainfall provides a wet environment for hyphal growth and development of arthrospores. A prolonged, moist environment would be typical along stream beds and their banks. *C. immitis* has been isolated from the air adjacent to a stream bed at Camp Roberts, California (Hoggen et al., 1956) and from soil near a dry stream bed and along dry washes (Swatek et al., 1967). Duran et al. (1973) reported an isolation of *C. immitis* from an arroyo and from the soil of a fertile river bottom abutting a drainage ditch. An increased deposition of salts near the surface of the soil, resulting from recent heavy rains, can provide a selective advantage to *C. immitis* (Elconin et al., 1964).

3.3 *Coccidioides immitis* and salt concentrations

Egeberg and Ely (1956) and Elconin et al. (1964) proposed that increasing salinity (e.g., CaCl_2 and NaCl) of surface soil in conjunction with elevated temperature, for example, 40 °C, would promote the growth and survival of *C. immitis*, inhibiting or killing microbial adversaries. The increasing salt concentration was

seen as the result of the leaching (solubilization) effect of heavy rains and subsequent movement of water and salts by capillary action toward the surface where evaporation would lead to deposition of the salts. Pappagianis (1988) found a selective effect of borate salts: at a concentration of 0.25% $\text{Na}_2\text{B}_4\text{O}_7$ in Sabouraud glucose agar, *C. immitis* prospered, and it grew to some extent at 0.5 and 1.0% concentrations. Neither *Histoplasma capsulatum* nor *Candida albicans* were able to proliferate at any of these concentrations of borate. Egeberg and Ely (1956) noted earlier the presence of high concentrations of boron salts in soils favored *C. immitis*.

3.4 *Coccidioides immitis* and pH

C. immitis is able to grow in vitro at a range of pH from 3.5 – 9.0. Although *C. immitis* did not grow abundantly at the extremes, contaminant or competing organisms appeared to be suppressed even more. Maddy (1957) observed that endemic areas are characterized by alkaline soil. Lacy and Swatek (1977) connected recovery of *C. immitis* from the soil of old American Indian middens to their sandy soils and alkalinity. *C. immitis* also favors soils containing substantial organic material, for example, rodent burrows (Egeberg and Ely, 1956) and in deserted mine tunnels containing bat guano (Kajihiro, 1965; Krutzsch and Watson, 1978).

3.5 Disturbed and cultivated soils

Several flare-ups of coccidioidomycosis have occurred after excavation of 'virgin' or at least long undisturbed, uncultivated soils (Maddy, 1957; Swatek et al., 1967; Werner and Pappagianis, 1973; Kafka and Catanzaro, 1981). Although occasional cases occur in agricultural workers, Pappagianis (1988) speculates that *C. immitis* might be forced into coping with a larger range of microbial competitors in cultivated and fertilized soil.

"The increase in primary coccidioidomycosis that occurs (in California) in late summer and fall rather than during the earlier springtime cultivation of the soil may be a result of the restriction of microbial competitors by heat, dehydration, and increasing salinity; the more abundant disarticulation and launching into the air of arthroconidia occurs in the relative dehydration of late summer and fall."

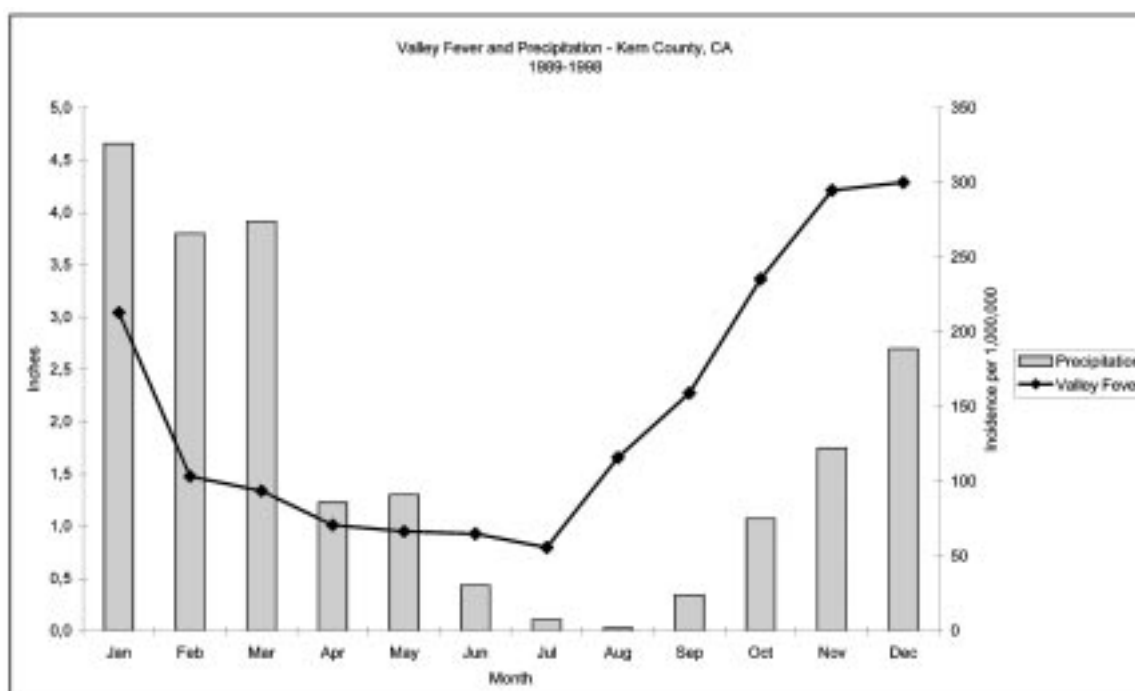


Figure 4. California's pattern of precipitation and valley fever incidence. (Source: National Climatic Data Center and California Department of Health Services.)

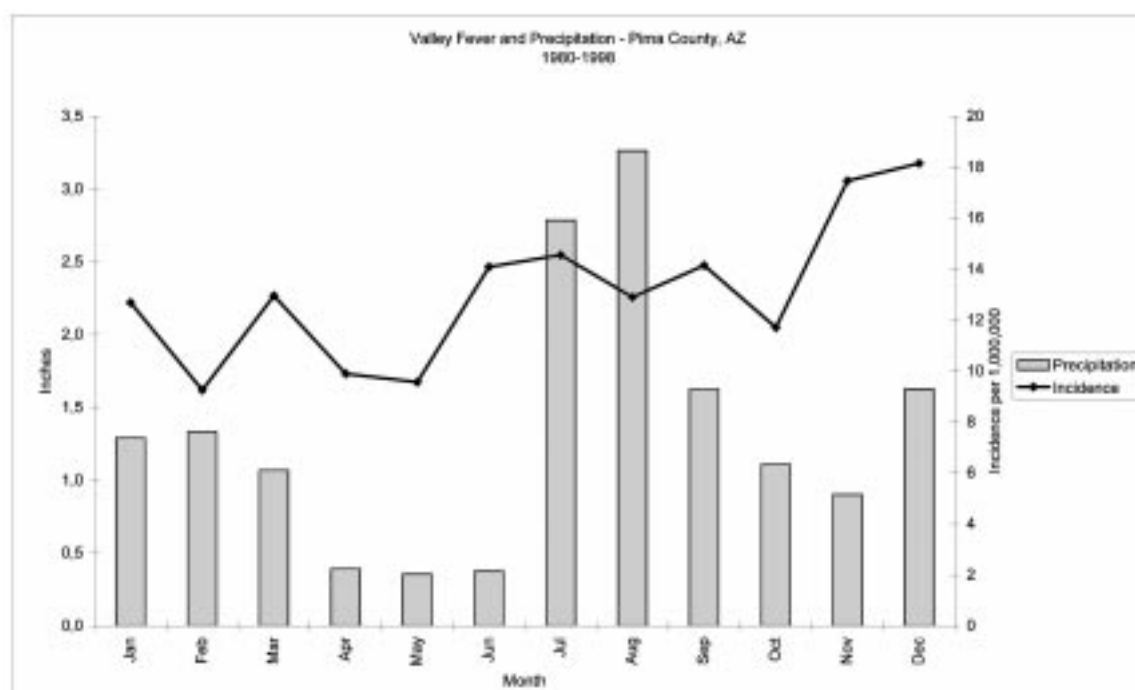


Figure 5. Arizona's bimodal precipitation pattern, and corresponding pattern of valley fever incidence. (Source: National Climatic Data Center and Arizona Department of Health Services.)

4. Future research directions

4.1 Future research on climate and *Coccidioides immitis*

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 Hugenholz in 1957 looked for a correlation between such information, but analyzed only fourteen years of data for a specific area (Hugenholz, 1957). 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. We recommend quantitative analysis of incidence data in conjunction with climate data, such as temperature, precipitation, wind speed, and relative humidity. An analysis of the entire endemic region in the United States will allow comparisons of different climatic regimes. An analysis of climate and valley fever incidence in California can, for example, be compared to the Arizona/New Mexico region. California receives the majority of its precipitation in winter (Figure 4), while the Southwest experiences a bimodal precipitation pattern (Figure 5). The two regions therefore have differing patterns of valley fever incidence, which may provide insight into the distribution of the fungus. 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.

4.2 Future research in soils and *Coccidioides immitis*

The fundamental problem is that it has not been possible to pinpoint one or a handful of surface variables that explain the geographic distribution of *C. immitis*. The theory developed by Elconin et al. (1964) and Egeberg et al. (1964) that soil salinity and temperature play roles in the mycology of *C. immitis* looks as if it is commonly acknowledged by other researchers (Sorensen, 1965; Swatek et al., 1965; Ajello, 1967;

Emmons et al., 1970). Though areas in the desert meet these requirements, many do not contain the fungus (Maddy, 1959). High salinity is characteristic of desert soil in general, but *C. immitis* is not distributed uniformly throughout these locations. It therefore appears that the true combination and importance of each variable has yet to be understood.

The literature on how multiple variables affect the spatial distribution of *C. immitis* in nature is sparse. Most research has focused instead on laboratory growth of typically singular or just a handful of environmental factors (Egeberg, 1962; Egebert et al., 1964; Elconin, 1963; Emmons, 1942; Guillemet and Montegut, 1960; Smith, 1972; Sorensen, 1965). Other studies have described where *C. immitis* has been isolated in the soil (Converse and Reed, 1966; Duran Jr. et al., 1963; Elconin et al., 1957; Fiese, 1958; Lacy and Swatek, 1974; Maddy, 1958; Maddy, 1964; Swatek and Plunkett, 1957). This lack of depth in the research on *C. immitis* motivates an integrative spatial modeling approach to describe the habitat of the fungus. A minimum set of variables for this would include: timing of wet and dry periods; soil moisture; soil temperature at various depths; soil texture and structure; vegetation cover and type; geochemistry (salinity); landuse (e.g., agricultural or residential); soil disturbance (areas where the soil is actively being thrown into the atmosphere) and the location of other animals (what animals have a role in the growth of the fungus). These variables might be used as the independent variables in a logistic regression model, with valley fever incidence data serving as the dependent variable. The results of the regression model predict probabilities of one state of the dependent variable. The method has been used successfully in several wildlife habitat studies (Pereira and Itami, 1991; Johnston, 1992; Mladenoff et al., 1995; Bian, 1997). Valley fever incidence data is used as a proxy for observed locations of *C. immitis*. This is an imperfect solution, and highlights the need for increased sampling of the soils in endemic areas to narrow the focus on where the fungus lives. The obvious method to accomplish this sampling is the field use of mobile polymerase chain reaction (PCR) machines, currently used by the United States military. These machines would enable soil samples to be taken and results obtained within minutes as to whether the soil is positive or negative for *C. immitis*.

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