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Assessment of Vulnerability to Coccidioidomycosis in Arizona and California

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Assessment of Vulnerability to Coccidioidomycosis in Arizona and California

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Abstract

Assessment of Vulnerability to Coccidioidomycosis in Arizona and California
By Jennifer Shriber

Introduction: Coccidioidomycosis is a fungal infection that is highly endemic in the southwestern United States, particularly in Arizona and California. Incidence has been rapidly increasing during the past decade due in part to changing climate pressures, particularly temperature and precipitation, on fungal growth and dissemination of spores. While most infected individuals experience no symptoms, severe manifestations can cause long-term morbidity and mortality. Various risk factors, such as age, ethnicity, and pre-existing conditions, make individuals more vulnerable to severe forms of the infection. This study aims to quantify county-level vulnerability to coccidioidomycosis and to assess any relationships between vulnerability and climate variability.

Methods: A vulnerability index was constructed for Arizona and California using indicators of susceptibility, exposure, and adaptive capacity. The index was validated using coccidioidomycosis incidence data from 2000-2014. Spearman rank correlation coefficients were calculated to assess significant associations between vulnerability index scores and temperature, precipitation, and drought index variability from the normal climate over this period of time.

Results: The vulnerability index was significantly correlated with coccidioidomycosis incidence in California ($P < 0.05$) but not Arizona. Based on the index, Cochise and Glenn Counties were the most vulnerable to coccidioidomycosis in Arizona and California, respectively. Moderate, positive significant associations ($p < 0.05$) were found between the coccidioidomycosis vulnerability index scores and climate variability scores when data for both California and Arizona were analyzed at the same time and when the California data were analyzed separately. No positive significant associations were found for Arizona data.

Discussion: The index performed moderately well at identifying vulnerable counties in California, but not Arizona. This may be due to the much higher incidence rates in Arizona, causing the general population to be vulnerable to infection despite the presence of documented risk factors. Findings from this study provide support for the hypothesis that climate variability is associated with coccidioidomycosis vulnerability. Limitations of this study include the coarse scale of data used, failure to capture mobile populations, and difficulties of assigning exposure indicators to mobile *Coccidioides spp.* spores.

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Introduction

Coccidioidomycosis, also known as Valley Fever, is a fungal infection arising from inhalation of *Coccidioides immitis* and *Coccidioides posadasii* spores [1]. It is endemic to the southwestern United States as well as parts of Mexico and Central and South America: in the United States, cases occur predominantly in Arizona and California [2, 3]. Inhalation of a single spore may be enough to cause illness, and approximately 40% of people who breathe in the spores experience symptoms that can range from mild (e.g. flu-like) to severe (e.g. community acquired pneumonia, meningitis, and disseminated infections) [4-6]. Risk factors for severe manifestations of coccidioidomycosis include age, weakened immune system, sex, and ethnicity [3, 7].

Coccidioidomycosis incidence has steadily increased in the American southwest over the past decade and a half with a peak in 2011 and a general decline thereafter; this trend has been particularly evident in Arizona and California [8]. Age-adjusted incidence rates in Arizona increased from 30.5 per 100,000 in 1998 to 247.7 per 100,000 in 2011, while age-adjusted rates in California increased from 2.1 per 100,000 in 1998 to 14.9 per 100,000 in 2011 [9]. The disease has a high financial burden: in Arizona alone, costs associated with coccidioidomycosis treatment totaled $59 million in 2007, with a median of $33,000 per individual hospital visit [10]. The disease is responsible for a loss of over one million person-days of labor per year in the United States [11]. Given this recent increase in coccidioidomycosis incidence, the identification of populations and locations that are vulnerable to increased incidence is vital in order to reduce the burden of this disease.

General Characteristics and Transmission

Coccidioides spp. are highly endemic in hot, arid to semi-arid environments in the Western Hemisphere. These regions are characterized by yearly rainfall ranging from 10-50 cm with extremely hot summers, winters with few freezes, and alkaline, sandy soil [12-14]. Outside of Arizona and California, in the United States *Coccidioides spp.* are also endemic in parts of Nevada, Texas, Utah, New Mexico, and Washington [6, 13, 15, 16]. *C. immitis* is generally endemic to California while *C. posadasii* ranges into Arizona and other parts of North America [16-18]. It was once believed that the two strains inhabited distinct regions; however, more recent studies demonstrate considerable overlap in the distribution of both species [6].

Coccidioides spp. are dimorphic fungi that grow as hyphae in the upper 5-20 cm of the soil [7, 16, 19]. The hyphae grow rapidly in the soil following periods of rain before developing into arthrospores during periods of drought or low precipitation [6, 11]. The arthrospores disarticulate into individual spores that become airborne and are dispersed due to natural conditions or anthropogenic soil disturbances, at which point they may be inhaled by human or animal hosts [6, 7, 11, 13]. The fungus transitions into its parasitic phase once inside the host. Increased heat and carbon dioxide concentration contribute to transformation of the arthroconidia into spherules in which endospores develop [13, 16]. The spherule can rupture and spread its contents, resulting in further distribution of infection throughout the body and allowing the parasite to repeat its life cycle [13, 16]. The most common mode of transmission is inhalation: however, rare cases of infection through fomites or transplanted organs have been recorded [13, 20].

Inhalation of a single spore can cause illness, and symptoms generally occur one to four weeks after exposure [10]. 60% of those who are infected experience mild to no symptoms [15]. The remaining 40% of infected people experience symptoms that can last for weeks to months [4]. The majority of experienced symptoms are flu-like, while 15% become very ill with pneumonia-like symptoms [21]. Less than 5% of infected people develop disseminated disease, during which the fungus spreads beyond the lungs and can infect other body sites including the bones, lymph nodes, and brain [15, 21]. This can lead to lifelong complications, as well as death. The most severe form of the disseminated disease is coccidioidal meningitis, the mortality from which is approximately 100% if untreated [11].

Incidence of coccidioidomycosis is dependent on a number of factors encompassing the environment, climate, human health, and human activity. A causal pathway is presented in Figure 1.

Susceptibility Factors for Severe Disease

Research has shown that several risk factors predispose individuals to severe or symptomatic coccidioidomycosis. Age is a well-documented risk factor, and many studies have documented that older populations are at higher risk [4, 13, 14, 22]. It is believed that individuals over the age of 65 are at particularly high risk of severe coccidioidomycosis, as they may have less robust immune systems or concurrent medical conditions that affect their overall health [4, 20, 22, 23]. Past studies have also shown higher risk among young children, especially those under the age of five [24]. Children are generally more vulnerable than adults to environmental risk due to a number of factors: most germane to coccidioidomycosis risk is their tendency to breathe more air in proportion to their weight and their differential exposure to dust and dirt [25].

Ethnicity has also been linked with risk to coccidioidomycosis. The risk of developing disseminated coccidioidomycosis is about 10-27 times greater in people of African-American and Filipino decent [7, 24, 26]. This has been linked to a genetic component that contributes to the development of disseminated disease [13, 27].

A wide range of health conditions, many of which compromise the immune system, increase risk for severe coccidioidomycosis. These include HIV/AIDS, cancer, organ transplantation, and dialysis [7, 11, 16, 20]. Individuals with diabetes may be at an increased risk of developing multiple thin-walled chronic lung cavities as a residual effect of infection [13, 16]. Pregnant women have also long been considered at risk of developing severe or disseminated coccidioidomycosis due to changes in levels of hormones that stimulate growth of the fungus [7, 28]. Preliminary studies in California have shown a link between smoking and risk of coccidioidomycosis infection, perhaps due to a suppression of the immune system [18, 22].

Occupations in which individuals are exposed to dust cause an elevated risk of coccidioidomycosis. This is especially true of professions that work with undisturbed earth, such as excavators or archaeologists [6]. Military personnel, construction workers, and agricultural workers have also been documented to be at higher risk of exposure and symptomatic disease [11, 13]. It is perhaps for this reason that males have also been found to have elevated risk of disease: males are more likely than females to have occupations that bring them into contact with dust, thereby leading to higher rates of coccidioidomycosis [14, 29]. A genetic link has been shown between sex and coccidioidomycosis, as Laniado-Laborin found that testosterone was highly stimulatory for the parasitic phase of *Coccidioides spp.* growth [7].

More generally, Cutter et al. describes a variety of factors that contribute to social vulnerability to environmental hazards and therefore would increase risk to diseases such as coccidioidomycosis [30]. Some of these – such as age, gender, and race – have already been discussed above. Additional characteristics include socio-economic status and educational attainment. Socioeconomic status affects an individual or community's ability to absorb losses and recover from shocks or hardships. This can also have an effect on personal health and wellbeing, as socioeconomic status is positively associated with health [31]. Education is linked to socioeconomic status, as higher educational attainment is associated with higher socioeconomic status and the resulting health benefits [30].

Environmental Risk Factors

Coccidioides spp. are endemic to many parts of the southwestern United States; however, certain environmental conditions are most conducive to fungus growth and exposure to spores. Certain types of soil have been associated with the growth of *Coccididoides* fungus. Nguyen et al. note that several studies in California found that the fungus appears more frequently in saline and alkaline soils [16]. This may be due to the role that high salinity plays in suppressing the development of antagonists [32]. In Arizona, meanwhile, *Coccidioides spp.* have been associated with rodent burrows and soil that is sandy, porous, hyperthermic arid or thermic arid, and semiarid [16, 19]. Hyperthermic soils are characterized by an average annual temperature less than 22°C at a depth of 50 cm; thermic soils have an average annual temperature from 15-22°C at the same depth [19]. Fisher et al. surveyed several known *Coccidioides spp.* sites in the southwest and noted that most sites contained very fine to fine sandy-sized soil with a notable fraction of silt [19]. While evidence of ideal soil types for *Coccidioides spp.* growth and development exists, this is based on a small number of studies and is therefore not conclusive.

While the type of soil can be beneficial for *Coccidioides spp.* growth, human uses of the land also contribute to risk of exposure. Studies have shown that there is an elevated risk of coccidioidomycosis incidence when virgin soil is disturbed in endemic areas, as soil disturbances allow *Coccidioides spp.* spores to become airborne and be inhaled by human or animal hosts. Oftentimes this is due to agriculture or construction, but outbreaks have also been associated with archaeological activity [6, 15, 33]. Fisher et al. have noted that areas with sparse vegetation are more favorable for growth, while cultivated fields and heavily vegetated, paved, or urbanized areas are less favorable [34].

Coccidioides spp. spores are only free to reach human and animal hosts once they are released from the soil. It is therefore understandable that dust and wind play an important role in coccidioidomycosis incidence. Dust has been associated with increased coccidioidomycosis incidence on numerous occasions and as a result of agriculture, construction, and dust storms [4, 7, 13, 15, 26, 35]. Wind has been linked to coccidioidomycosis incidence, including outbreaks following dust storms [36, 37].

Climate Drivers of Coccidioidomycosis

Coccidioides spp. follow “grow and blow” stages of development. First, the fungus requires precipitation in order to grow in the soil. Many studies have demonstrated this link between precipitation and coccidioidomycosis. Comrie (2005) found that precipitation one and a half to two years prior was associated with increased incidence in Pima County, Arizona [1]. Other studies also noted moderate to high correlations between incidence and antecedent precipitation in Arizona [11, 26]. This link is strong in Arizona; however, studies performed in California have found weak correlations between coccidioidomycosis and precipitation [18, 38]. While precipitation is needed for fungus growth, too much can be harmful. Kolivras et al. (2001) note that competitors may prevail if conditions are too moist [14]. *C. immitis* prevalence generally decreases in climates with average precipitation rates of less than 10 cm per year or greater than 50 cm per year [14].

The “blow” stage refers to spore development and dissemination during dry periods. In both Arizona and California, coccidioidomycosis is most frequently reported during dry months. In Arizona, this is generally in late fall and spring, at the end of the dry period [4, 28]. California, meanwhile, sees increased numbers of cases during the dry summer months and fall following the winter and spring rains [20, 24, 38]. Numerous studies found that lower antecedent rainfall was significantly associated with increased incidence of symptomatic coccidioidomycosis in Arizona [1, 5, 11, 26, 35, 36, 39]. Still others found positive associations between antecedent drought and increased coccidioidomycosis incidence in both Arizona and California [4, 26, 39]. As noted previously, particulate matter and wind velocity have also been linked to coccidioidomycosis, providing more evidence for the importance of dispersion-related conditions in the spread of coccidioidomycosis [1, 4, 11, 26, 38, 40].

Further associations have been found between antecedent temperature and coccidioidomycosis incidence [4, 11, 26, 39]. Higher temperatures during the early stages of growth cause sterilization of the soil, thereby removing competitors while spores remain viable below the surface [11].

Population Vulnerability to Climate Change & Climate Variability

The southwestern United States is uniquely affected by climate change and climate variability. The Inter-Governmental Panel on Climate Change (IPCC) defines climate change as “a change in the state of the climate that can be identified…by changes in the mean and/or the variability of its properties, and that persists for an extended period, typically decades or longer [41].” Climate variability, meanwhile, refers to “variations in the mean state and other statistics of the climate beyond that of individual weather events” [41]. Climate variability, as a component of broader climate change, can deal with climatic change on a smaller time scale by looking at seasonal differences between years or other temporal scales.

The southwestern region is currently warming, and average daily temperatures for the 2001-2010 decade were the highest in the southwest from 1901 through 2010 [2]. Recent droughts have also been unusually severe as compared to droughts in the region during the last century [2]. Projected future climatic changes for the southwest include continued warming, decreased precipitation, and more frequent and severe droughts [2]. These changes will occur among a rapidly increasing population: the current southwestern population is expected to increase by 19 million by 2030 [2]. As a result, a large number of people will be at risk of the negative health effects associated with a changing climate, including increased coccidioidomycosis incidence.

This increased risk is not uniform, however. Different groups of people are more adversely affected than others depending on their vulnerability to climate-related health impacts. The IPCC's Fourth Report defines vulnerability as a function of "the character, magnitude, and rate of climate change and variation to which a system is exposed, the sensitivity and adaptive capacity of that system" [42]. This definition has since been updated to exclude exposure, although exposure continues to be considered a primary constituent of vulnerability in other academic circles. These three concepts – exposure, sensitivity, and adaptive capacity – are crucial to understanding vulnerability to climate change and its effects on human health [43]. The most vulnerable groups are those that are most exposed to environmental hazards, that are most susceptible to the negative effects of those hazards, and that are least resilient to recovery [44].

Exposure refers to "the presence of people, livelihoods, species or ecosystems, environmental functions, services, and resources, infrastructure, or economic, social, or cultural assets in places and settings that could be adversely affected" [43]. The health of a population reflects, among other things, its environmental living conditions [45]. Proximity to an environmental hazard, or to conditions conducive to a particular hazard, increases the vulnerability of even the most privileged communities. In terms of vulnerability to increased incidence of coccidioidomycosis, this represents conditions that are conducive to the growth and spread of fungus within the environment.

Exposure alone does not determine vulnerability: vulnerability of a place includes not only the physical exposure to a hazard but also the susceptibility to such a hazard. The IPCC defines susceptibility to climate change as “the degree to which a system or species is affected, either adversely or beneficially, by climate variability or change” [42]. People or groups that are socially, economically, culturally, politically, institutionally, or otherwise marginalized are especially vulnerable to the effects of climate change [46]. As mentioned previously, certain groups that are more susceptible to illness or that have lower socio-economic status are disproportionately vulnerable to hazards including the spread of coccidioidomycosis [2]. A place or community’s adaptive capacity mitigates this susceptibility. Access to adequate resources, systems, or institutions can allow communities to adjust to potential hazards and respond to actualized hazards, thereby reducing their vulnerability [47].

Assessing Vulnerability

Identifying groups or places that are vulnerable to climate change is an important step in mitigating human health risks from climate change. The Climate and Health Program (CHP) at the Centers for Disease Control and Prevention (CDC) has developed the five-step Building Resilience against Climate Effects (BRACE) framework to help health departments prepare for and respond to climate change. The first step of this framework focuses on anticipating climate impacts and assessing health vulnerabilities associated with climate change [48].

Many studies have been undertaken to assess vulnerability to environmental hazards and climate change [30, 44, 45, 49-62]. Vulnerability assessments encompass a diverse set of methods used to systematically integrate and examine interactions between humans and their physical and social surroundings [54]. Vulnerability assessments allow for the conceptualization of a complex array of factors and interactions that lead to vulnerability. Rather than focusing on the likelihood of a particular hazard occurring, these assessments instead analyze the factors that impact exposure, susceptibility, and ability to adapt to a hazard [52]. This is often accomplished by the creation of an index that assigns numeric scores to particular locations based on indicators of these three vulnerability components.

Vulnerability assessments in general, and vulnerability indices in particular, allow for the use of a rich array of datasets and models to holistically describe the vulnerability of a place or community, and serve as useful tools for policy and adaptation efforts. However, researchers and policymakers must be careful when creating and interpreting them. Like all statistical models, vulnerability indexes are imperfect and do not reflect the reality that they seek to convey [63]. The use of indicators to represent complex phenomena leads to simplification at best and gross inaccuracy at worst. Additionally, assessing vulnerability on a large scale can mask the specific risks of particular locations [63]. Nevertheless, assessing vulnerability through the creation of carefully thought-out indices can provide important information for identifying and protecting vulnerable populations.

Purpose of Study

The purpose of this study is to assess the vulnerability of counties in Arizona and California to increased incidence of coccidioidomycosis resulting from changing climate. The specific aims of the study are twofold: (1) to describe counties’ vulnerability to coccidioidomycosis based on indicators representative of exposure, susceptibility, and adaptive capacity; and (2) to examine the association between vulnerability and deviation from normal climate in these counties. A variety of studies have been conducted to determine environmental risk factors for coccidioidomycosis. However, there has at present been no effort to identify locations that are particularly vulnerable to the disease. This study will improve the understanding of vulnerability to coccidioidomycosis and will provide a tool that can be used to guide future adaptation strategies.

Methods

Data Collection

For the purposes of this study, vulnerability was defined using the IPCC's Fourth Report definition, which gives vulnerability to climate change as the following function:

Vulnerability = Exposure + Susceptibility – Adaptive Capacity [42]

Indicators of susceptibility, environmental exposure, and adaptive capacity were selected based on the literature and availability of data. Table 1 presents an overview of the indicators used for the vulnerability index. All data were tabulated by county in ArcGIS 10.3.1 using TIGER/Line Shapefiles and the GCS North American 1983 projection [64, 65].

Susceptibility variables represent conditions that predispose individuals to coccidioidomycosis and illness in general. The majority of susceptibility variables – percent of population above 65 years, percent of population below 5 years, percent of African Americans and Filipinos, percent of adult population that has not completed a higher education degree, and percent under the poverty level – were obtained from the

2010 United States Census. Educational attainment and poverty were included in the index as they are general indicators of vulnerability, as elucidated by Cutter et al. (2003) [30]. Percentage of the populations living with HIV/AIDS and percent of the adults who smoke were supplied by the Centers for Disease Control and Prevention (CDC), while cancer incidence rates were obtained from the National Cancer Institute [66-68].

Land data representing exposure to *Coccidioides spp.* came from the Multi-Resolution Land Characteristics Consortium National Land Cover Database [69]. These data were used to represent counties' suitability for *Coccidioides spp.* growth and development. Suitability calculations for these data are presented in the 'Descriptive Analysis' section.

Adaptive capacity was represented by the number of hospitals per county and the number of primary care physicians per 100,000 people for each county. These represent the capacity of each county to diagnose and treat infected individuals. Hospital data were obtained from the American Hospital Association [70]. The number of primary care physicians for each county was obtained from the Health Resources and Services Administration's 2012 Areal Resource File [71].

Coccidioidomycosis case counts were provided by the Centers for Disease Control and Prevention (CDC) Mycotic Diseases Branch. Coccidioidomycosis has been a nationally notifiable disease since 1995, and cases from Arizona and California meeting the Council of State and Territorial Epidemiologists (CSTE) case definition of laboratory and clinical confirmation of infection were included (see Appendix 2 for complete case definition). Case counts for some California counties were very sparse and were therefore not included.

Climate data were obtained from the National Oceanographic and Atmospheric Administration (NOAA) National Centers for Environmental Information (NCEI) [72]. Monthly minimum, maximum, and average temperature, precipitation, and drought index (Standardized Precipitation-Evapotranispiration Index, SPEI) were downloaded for all weather stations within California and Arizona for the period of 2000-2014. Normal monthly climate data, including standard deviations, spanning the period of 1981-2010 were also downloaded from the NCEI [73].

Descriptive Analysis

Descriptive statistics for the data were generated in R [74]. These were displayed graphically and mapped in order to visually assess any patterns or trends.

Monthly and annual county population estimates from the US Census were used to calculate coccidioidomycosis incidence rates per 100,000 people. Monthly case counts were lagged by one month to take into account reporting delays [10, 21]. Where monthly population estimates were missing, linear interpolation was performed to calculate these data. Inter-annual and intra-annual coccidioidomycosis incidence rates for Arizona and the California counties in which case data was available were then plotted graphically. Moran's I and LISA statistics were computed to assess any clustering of coccidioidomycosis incidence rates among counties.

Correlations between the vulnerability index variables and coccidioidomycosis incidence rates were assessed using Spearman correlation coefficients. Land cover type raster data were categorized into a binary variable based on criteria noted by Fisher et al. (2007), with 0 being unsuitable for *Coccidioides spp.* growth and 1 being suitable for growth [19]. Developed, open space; barren land; shrub/scrub; and grassland/herbaceous categories were assigned a '1,' while all other land types were designated as '0.' The land cover suitability variable represented the percent of raster points in each county with an assignation of '1.' The 2010 geographic area of each county was used to calculate the number of hospitals per 100 square miles.

Precipitation, temperature, and SPEI data were aggregated to the county level and seasonal and annual minimum, maximum, and average values were computed. Standard deviations for the normal climate data were used to calculate Z scores at the county level in order to indicate by how many standard deviations the seasonal climate indicators for the study period varied from the normal climate in each county during the study period. Choropleth maps were constructed in ArcGIS to visually display the climate Z scores for each season. Inter-annual and intra-annual climate data was also plotted graphically for each state.

Coccidioidomycosis Vulnerability Indices

ArcGIS was used to assign composite vulnerability scores for susceptibility, exposure, and adaptive capacity index components for each county. Indicators representing each component were summed to create intermediate susceptibility, exposure, and adaptive capacity components by county. Three approaches were used to create the indices: (1) principal components analysis; (2) quartile scoring; and (3) percentile scoring. The principal components analysis was completed in R to collapse the index variables into several interpretable underlying factors, which could then be assigned scores based on their values. The quartile scoring method assigned values to each indicator based on quartiles for each state. County-level indicator values falling into the first, second, third, or fourth quartile for each state received a value of 0.25, 0.5, 0.75, or 1, respectively. The percentile scoring method used state percentiles to score each indicator, with a maximum value of 100.

The adaptive capacity score was made negative to reflect the reduction of vulnerability caused by increased adaptive capacity. The component scores were in turn summed to construct the overall vulnerability score. Equal weighting was given to each indicator within a component, as well as to the components themselves. Equal weighting was assumed as no evidence from the literature was found to support other methods of weighting. An additive model was chosen for the index based on the use of this model in other studies [30, 47, 56]. This was deemed a better choice than a multiplicative model, as the latter would assign a vulnerability index score of zero to any county that may have a susceptibility, exposure, or adaptive capacity score of zero, thereby nullifying the other index components. In an attempt to increase accuracy, two sets of indices were created. The first assigned variables to susceptibility, exposure, and adaptive capacity components based on findings from the literature. Modified indices were also created using the results of the correlations between index variables and coccidioidomycosis incidence: while percent of suitable land per county remained the sole variable for exposure, all variables with negative correlations were classified as adaptation variables and all variables with positive correlations were included in the susceptibility component.

The vulnerability indices were validated by computing Spearman rank correlation coefficients to assess linear associations between the index scores and coccidioidomycosis incidence rates at the county level. Annual, seasonal, and 15-year coccidioidomycosis incidence rates were used for the validation exercise. As incidence data were not available for some California counties, these were excluded from the validation data. Monte Carlo simulation Moran's I and Anselin Local Moran's I statistics were computed for the best-performing index to assess any clustering of vulnerability among counties.

Climate Variability & Coccidioidomycosis Vulnerability

Climate variability was used as an indicator of broader climate change for the purposes of this study: climate variability provided an indication of how coccidioidomycosis responds to climatic changes given the relatively short data records available. For each county, standard deviations of normal climate data were used to calculate the Z scores for seasonal, annual, and overall temperature, precipitation, and SPEI. The absolute values of the climate Z scores were summed to produce seasonal and overall climate variability scores. These scores indicate any deviations of the 2000-2014 study period values from the baseline normal (1981-2010) temperature, precipitation, and SPEI: higher deviations indicate higher exposures to changes in climate [56]. Spearman correlation coefficients were calculated to assess any linear relationships between the vulnerability index score and climate variability score for each county.

Results

Descriptive Analysis

Inter- and intra-annual coccidioidomycosis incidence rates are presented in Figures 2 and 3. Coccidioidomycosis incidence rates are substantially higher in Arizona as compared to California. During the 2000-2014 period, Arizona had a maximum incidence rate of 259.50 per 100,000 (2011), a minimum of 37.46 per 100,000 (2000), and a mean of 102.40 per 100,000. California, meanwhile, had a maximum incidence rate of 19.71 per 100,000 (2011), a minimum of 3.09 per 100,000 (2000), and a mean of 9.84 per 100,000. In both states, incidence increased substantially starting in 2000 before decreasing from 2011 onwards. Plotting average incidence rates for each month across the 2000-2014 study period revealed rising incidence rates in spring and fall. November had the highest incidence rate for both Arizona and California – 13.64 per 100,000 and 1.81 per 100,000, respectively – while Arizona's minimum incidence rate occurred in August (7.88 per 100,000) and California's occurred in January (0.59 per 100,000).

Moran's I indicated positive global spatial autocorrelation of the average annual incidence (2000-2014) in both states, with similar values tending to cluster together throughout each state. In Arizona, local clusters of high 2010 and average annual incidence rates were located in the southern counties of Maricopa, Pinal, and Pima. Local clustering was only apparent in California for average seasonal incidence: Los Angeles and Orange counties in the southern part of the state had clusters of high average fall, spring, summer, and winter coccidioidomycosis incidence.

Spearman correlation coefficients assessing any linear relationships between the index variables and coccidioidomycosis incidence rates are presented in Tables 2 and 3. Analyzing the Arizona and California data together, there are significant linear relationships between coccidioidomycosis incidence and the percent of the county population of Filipino descent, percent of the population below poverty level, cancer incidence rate, percent adults who smoke, percent of adults with no higher education, primary care physicians per 100,000 per county, and hospitals per 100 square miles per county. We observed a negative linear relationship between incidence rates and percent African American population, percent Filipino population, cancer incidence rates, and percent people living with HIV/AIDS.

Varying significant relationships were observed in each of the states when they were analyzed separately. In Arizona, significant linear relationships were only observed between coccidioidomycosis incidence and percent of the population living with HIV/AIDS and the number of hospitals per 100 square miles. The direction of the linear association between percent of population below five years, percent below poverty level, percent with no higher education, and number of hospitals per 100 square miles and coccidioidomycosis incidence was contradictory to the expected relationships from the literature. Correlations for the California data largely mirrored that for the combined data set, with the exception of significant linear associations with the two age variables.

Figures 4-6 show climate trends for Arizona and California spanning the 15-year study period. Significant variability is evident among the annual mean, maximum, and minimum precipitation and SPEI in both states; temperature, meanwhile, has stayed relatively constant during the 15-year span. While intra-annual temperature follows the same patterns in both states (Figure 7), with peaks in the summer and low points in December, there is much variability in terms of precipitation and SPEI (Figures 8 and 9). Arizona receives the most precipitation during the summer months: accordingly, its SPEI also peaks during these months. California, meanwhile, experiences the most rain during the late fall and winter. Intra-annual SPEI values for California reflect this trend.

Climate variability scores were calculated cumulatively, seasonally, and individually per climate variable (temperature, precipitation, and SPEI). Figure 10 displays a choropleth map of the overall climate variability scores for each county: the northern Del Norte County and central Madera and Tuolumne counties experienced the most overall variability from climate normal during the period of 2000-2014, while Pinal County, located in southern Arizona, experienced the most climate variability in that state. Arizona experienced more overall climate variability than California; one can observe in Figures 11-17 that Arizona counties had more overall seasonal variability, as well as variability in terms of temperature, precipitation, and SPEI throughout the study period. For both states, the highest average overall seasonal variability was observed in the fall, while the lowest was in the spring for California and the winter for Arizona. Additionally, the temperature accounted for the highest amount of variability for both states across the entire study period.

Coccidioidomycosis Vulnerability Indices

A total of four indices – quartile and percentile indices based on both the literature and variable correlations – were created for each state: principal component analysis results were not meaningful and this method was therefore not used to create additional indices. The validation results are presented in Table 4. The modified percentile index performed the best in all cases. There were significant correlations between this index and most iterations of coccidioidomycosis incidence when validated using data from both states combined and data from California only. The modified quartile index was also significantly correlated with incidence for both states combined and California only, while the two literature-based indices were positively correlated with some incidence data for California only. There were no significant correlations between vulnerability index scores and coccidioidomycosis incidence for Arizona; however, the modified percentile index had the highest Spearman rank correlation coefficients for all forms of incidence.

Figure 18 displays the coccidioidomycosis vulnerability index scores based on the modified percentile index, which performed best for both states. In Arizona, index scores ranged from -31.0 (Apache County, located in the northeast) to 127.3 (Cochise County, in the southeast), with a mean of 47.3 and a standard deviation of 56.6. In California, meanwhile, scores ranged from -65.6 on the northern coast (San Francisco County) to 128.6 farther north and inland (Glenn County), with a mean of 49.8 and a standard deviation of 46.2. Figures 19 and 20 present the index scores based on quartiles for each state. Based on the indices, Mohave and Cochise counties – located in the far southeast and northwest, respectively – are most vulnerable to increased coccidioidomycosis incidence in Arizona. Meanwhile in California most of the southern counties and the more central counties of Del Norte, Lassen, Tehama, Glenn, Colusa, and Alpine are the most vulnerable counties.

The coccidioidomycosis vulnerability index scores were positively globally autocorrelated both when considering the two states together and when looking at California separately. Local autocorrelation was present for the two states combined, as well as both Arizona and California separately. The majority of local autocorrelation was clustering of low-low values: in California this can be seen in the counties surrounding San Francisco, while in Arizona clustering of low index scores was present around

Navajo County in the northeast. When both Arizona and California were considered together, clustering of high scores was present across the state border in La Paz (Arizona) and Imperial (California) counties.

Climate Variability & Coccidioidomycosis Vulnerability

The Spearman rank correlation coefficients assessing correlation between vulnerability scores and climate variability can be seen in Table 5. When comparing the vulnerability scores for counties in both states combined, there were significant linear associations with most of the climate variability scores (with the exception of fall and winter temperature and SPEI variability). It is interesting to note that there is a negative association between all seasonal precipitation variability scores and vulnerability index scores. The Arizona index scores were significantly correlated with fall precipitation variability, overall spring variability, and spring temperature variability scores; again, these were all negatively correlated. The California index was significantly correlated with most of the climate variability scores. While most of the correlations with precipitation variability scores were negative, the rest of the variability scores were positively correlated with the vulnerability index scores.

Discussion

Spearman correlations between the coccidioidomycosis vulnerability index variables and incidence rates yielded results that were unexpected given the literature on coccidioidomycosis risk factors. While age, ethnicity, and pre-existing medical conditions (cancer and HIV/AIDS) have been documented to increase the risk of severe coccidioidomycosis, these factors had a negative correlation with incidence in either Arizona or California separately or both states combined. One reason for these results may be the small percentage of the population that is made up of people with these characteristics. In most counties included in this study, for example, Filipinos make up only 0.01%-1.60% of the population. Even though people of Filipino ethnicity are at a higher risk for coccidioidomycosis, their scarce numbers may not substantially contribute to the vulnerability of the county as a whole. Additionally, the high incidence rates in Arizona in particular could mask any individual risk factors. Since the disease is highly endemic throughout the state, individuals are at risk regardless of their individual characteristics or risk factors. This may explain the lack of significant correlations between the Arizona index variables and incidence rates, as well as the non-significant validation results for the Arizona coccidioidomycosis vulnerability index.

Reorganizing the vulnerability index variables based on the correlation results produced an index that represents vulnerability to coccidioidomycosis reasonably well. The selected vulnerability index was significantly correlated, albeit weakly, with all forms of coccidioidomycosis incidence when both Arizona and California data were considered together. The index performed better when considering California only, as a moderate linear relationship was displayed between the index scores and most forms of coccidioidomycosis incidence. The index accurately captured the high vulnerability in the San Joaquin Valley, located centrally within the state, as well as the low vulnerability in the San Francisco area and parts of northern California. The index performed less well in Del Norte, Modoc, Tehama, Glenn, and Colusa counties: while these counties received high vulnerability index scores, their climate and geography make them ill-suited for coccidioidomycosis and they report few to no cases each year. The index did not perform well in Arizona, as there were no significant linear relationships between the index scores and incidence (moderate non-significant relationships were reported for most forms of incidence, however). The southern Arizona counties of Pinal, Pima, and Maricopa were correctly assigned high vulnerability index scores that matched their high incidence rates. As stated above, this could be due to the fact that high incidence in the state puts everyone at risk regardless of individual or population characteristics.

While Arizona is known to have much higher incidence rates than California, it was interesting to note that the mean index score was higher for the state of California. This lack of accord between the vulnerability scores and incidence rates suggests that other factors play a role in coccidioidomycosis vulnerability. *Coccidioides spp.* require specific habitats and climate conditions to thrive. It is possible that counties with high vulnerability scores but low incidence rates lack the proper characteristics for fungus growth and spore dissemination. Similarly, counties with low vulnerability scores and high incidence may see more cases because they are better suited to *Coccidioides spp* despite lacking in the realm of susceptibility factors.

Findings from this study provide support for the hypothesis that climate variability is associated with coccidioidomycosis vulnerability. The California data shows significant positive linear relationships between index scores and climate variability, particularly variability in the spring, summer, and fall. The same can be seen when considering data from Arizona and California together. Arizona data was largely not significant; this could once again be due to the saturated of coccidioidomycosis in the state that masks underlying trends. While precipitation variability was negatively correlated with index scores, this could be due to the fact that precipitation conditions can both help and hinder *Coccidioides spp.* growth and dissemination. Dry conditions are essential for spore dissemination; however, initial moisture is needed for the fungus to grow per the "grow and blow" hypothesis. Therefore variability in the form of too much or too little rain would impede the spread of *Coccidioides spp.* spores. The results demonstrate that counties with high climate variability – whether in terms of temperature, SPEI, or overall seasonal climate variability – are more vulnerable to coccidioidomycosis incidence. Additional research into the causal mechanism of climate and coccidioidomycosis could further clarify this relationship.

Limitations

This index is mainly limited by its geographic scale. *Coccidioides spp.* are highly affected by climate and environmental pressures that occur at very fine geographic scales. This index was created at the county level due to availability of data; as such, it fails to capture place-specific fluctuations within each county. Generalization, while necessary given the geographic scope of the socio-demographic data used for the index, can mask trends that occur at s smaller scale. This is true not only for environmental data but also for the variables that were used as indicators of susceptibility. A finer index that can identify sub-county pockets of vulnerability would prove most useful for identifying populations that are at risk of rising coccidioidomycosis incidence rates; however, this may also have high uncertainty due to small numbers.

Additionally, the mobile nature of people means that some information bias may be present regarding the county of infection. Incidence data fails to capture mobile populations in the two states, particularly migrant workers and older individuals who travel to the area for the winter. Since the coccidioidomycosis case counts were based on location of residence, the case count information may not accurately represent the county in which people were infected.

Finally, the nature of coccidioidomycosis epidemiology made it difficult to assign indicators of exposure. *Coccidioides spp.* spores can travel long distances once they are airborne, and as such the presence of suitable conditions in one location does not guarantee higher exposure in that area. Future vulnerability indices would be strengthened by the use of exposure indicators that can take spore movement into account.

Conclusions

Coccidioidomycosis is highly endemic in the southwestern United States, particularly in Arizona and California. Incidence has been rapidly increasing due in part to changing climate pressures that affect the fungus's growth and dissemination of spores. A vulnerability index was created using indicators of susceptibility, exposure, and adaptive capacity for counties in Arizona and California. This index visually displays the counties that are most at risk of increased coccidioidomycosis incidence. Analysis also demonstrated a significant positive linear relationship between climate variability and vulnerability to coccidioidomycosis at the county level. This research adds to the body of knowledge that could be used to target adaptation measures to the most vulnerable counties. Future research is needed better capture vulnerability in Arizona and to display vulnerability at a finer geographic scale for both Arizona and California.

Appendix 1: Figures and Tables

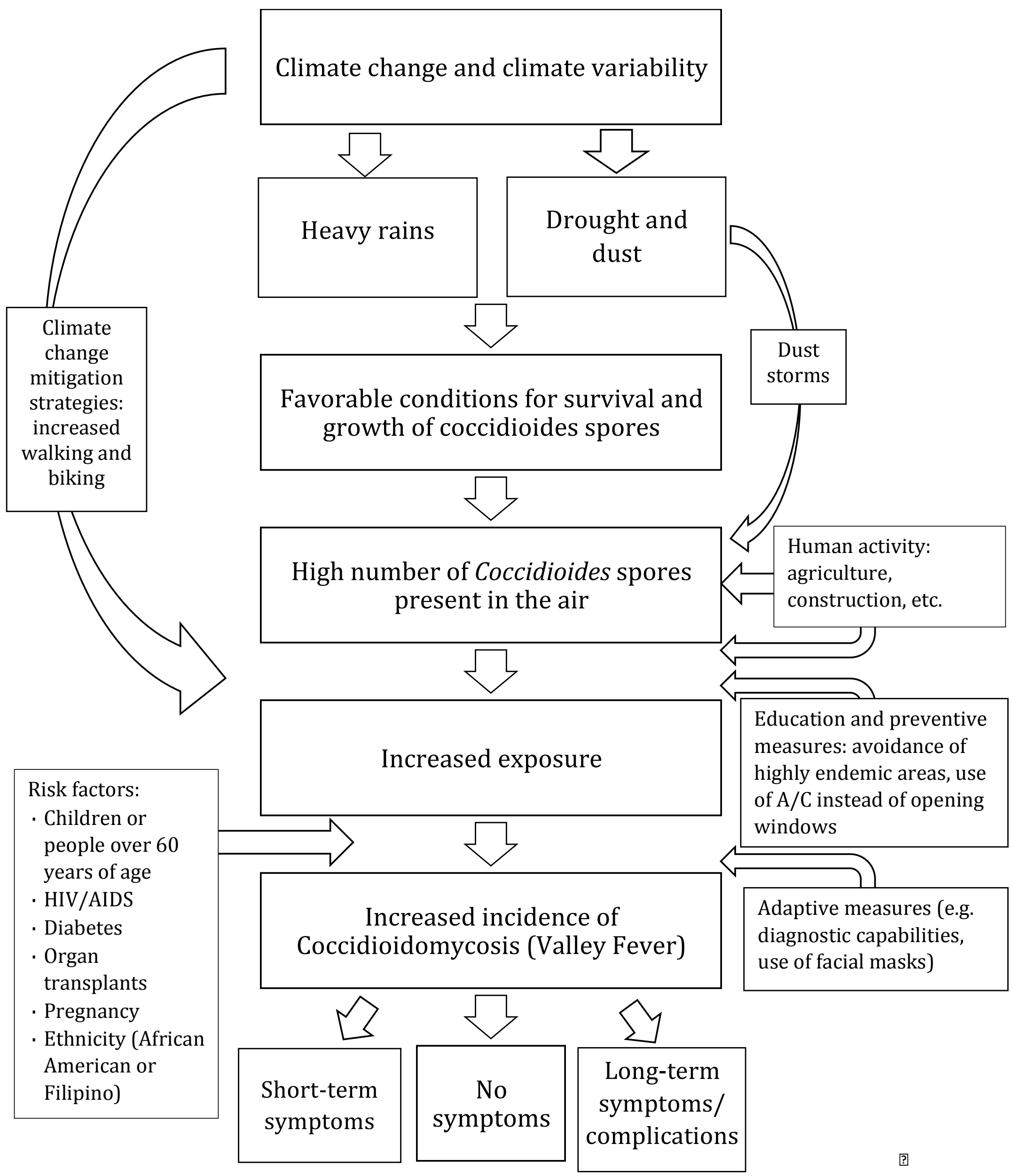

Figure 1: Causal Pathway of Coccidioidomycosis. *The coccidioidomycosis causal pathway includes both environmental and anthropogenic drivers. Risk factors play a large role in the severity of infection.*

Table 1: Vulnerability Index Indicators

Indicator	Source (Year)
Susceptibility	
Percent of Population > 65 years	US Census (2010)
Percent of Population < 5 years	US Census (2010)
Percent of Population of African American Race	US Census (2010)
Percent of Population of Filipino Race	US Census (2010)
Percent of Population Below Poverty Level	US Census (2010)
Percent of Population with No Higher Education	US Census (2010)
Percent of Population Living with HIV/AIDS	CDC National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention (2012)
Cancer Incidence Rate Per 100,000 (All Types)	National Cancer Institute (2012)
Percent of Adults Who Smoke	CDC Behavioral Risk Factor Surveillance System (2010)
Exposure	
Percent of Land Suitable for *Coccidioides spp.* Growth	Multi-Resolution Land Characteristics Consortium (2011)
Adaptive Capacity	
Number of Hospitals Per 100 Square Miles	American Hospital Association (2012)
Number of Primary Care Physicians Per 100,000	HRSA Areal Health Resource File (2012)

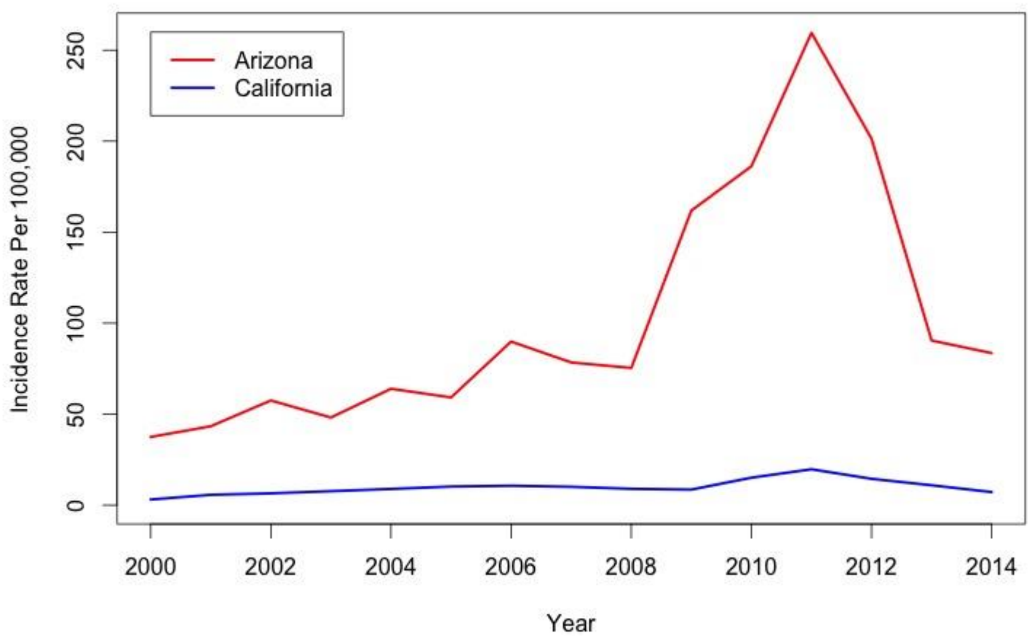

Figure 2: Inter-Annual Coccidioidomycosis Incidence Rates. *Coccidioidomycosis rates have risen since 2000 in both states, culminating in a peak in 2011.*

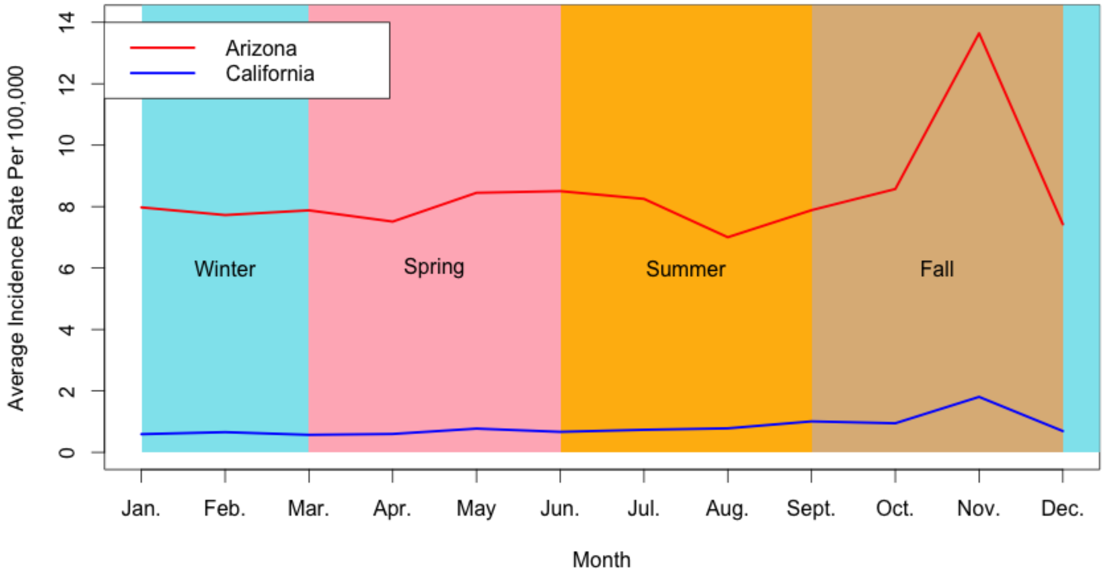

Figure 3: Intra-Annual Coccidioidomycosis Incidence Rates. *Incidence rates in both states peak in November. Arizona incidence peaks in the late spring/early summer and fall, while California incidence is highest in the summer and fall.*

Table 2: Spearman Rank Correlation Coefficients for Vulnerability Index Variables and Coccidioidomycosis Incidence: Arizona and California Combined

	Mean Annual Incidence Rate	2010 Incidence Rate	Mean Fall Incidence Rate	Mean Spring Incidence Rate	Mean Summer Incidence Rate	Mean Winter Incidence Rate
% 65+	0.17	0.11	0.14	0.19	0.15	0.17
% <5	0.24	0.27	0.24	0.22	0.24	0.20
% African American	-0.26	-0.25	-0.27	-0.27	-0.27	-0.27
% Filipino	-0.55	-0.55	-0.54	-0.55	-0.55	-0.53
% Below Poverty Level	0.44	0.51	0.43	0.45	0.45	0.44
Cancer Incidence Rate	-0.52	-0.53	-0.50	-0.52	-0.51	-0.51
% Adults Who Smoke	0.32	0.35	0.33	0.37	0.33	0.31
% PLWHA	-0.18	-0.20	-0.19	-0.20	-0.19	-0.18
% Adults with No Higher Education	0.46	0.47	0.43	0.46	0.47	0.44
% Suitable Land	0.23	0.25	0.22	0.24	0.19	0.22
PCPs Rate	-0.52	-0.53	-0.49	-0.53	-0.50	-0.50
Hospitals Per 100 Sq. Mi.	-0.47	-0.49	-0.46	-0.47	-0.47	-0.45

Gray indicates $p < 0.05$
All Rates Are Per 100,000
PLWHA = People Living with HIV/AIDS
PCP = Primary Care Physician

Table 3: Spearman Rank Correlation Coefficients for Vulnerability Index Variables and Coccidioidomycosis Incidence: Arizona and California Separately

	Arizona Only						California Only					
	Mean Annual Inc. Rate	**2010 Inc. Rate**	**Mean Fall Inc. Rate**	**Mean Spring Inc. Rate**	**Mean Summer Inc. Rate**	**Mean Winter Inc. Rate**	**Mean Annual Inc. Rate**	**2010 Inc. Rate**	**Mean Fall Inc. Rate**	**Mean Spring Inc. Rate**	**Mean Summer Inc. Rate**	**Mean Winter Inc. Rate**
% 65+	0.13	0.13	0.09	0.22	0.12	0.21	-0.47	-0.55	-0.49	-0.50	-0.53	-0.45
% <5	-0.13	-0.14	-0.19	-0.21	-0.17	-0.21	0.65	0.70	0.68	0.68	0.67	0.58
% African American	0.46	0.42	0.40	0.41	0.37	0.40	-0.20	-0.19	-0.24	-0.18	-0.17	-0.20
% Filipino	0.36	0.36	0.33	0.35	0.30	0.32	-0.46	-0.50	-0.53	-0.47	-0.45	-0.40
% Below Poverty Level	-0.36	-0.24	-0.40	-0.38	-0.36	-0.30	0.66	0.72	0.68	0.70	0.68	0.64
Cancer Inc. Rate	0.28	0.20	0.33	0.29	0.28	0.26	-0.51	-0.50	-0.52	-0.48	-0.51	-0.45
% Adults Who Smoke	0.15	0.16	0.11	0.22	0.16	0.20	0.17	0.23	0.20	0.23	0.19	0.12
% PLWHA	0.49	0.58	0.41	0.45	0.41	0.49	-0.27	-0.33	-0.31	-0.27	-0.27	-0.25
% Adults with No Higher Education	-0.24	-0.22	-0.25	-0.25	-0.22	-0.23	0.69	0.76	0.68	0.73	0.71	0.65
% Suitable Land	0.22	0.26	0.11	0.20	0.10	0.31	0.07	0.05	0.11	0.05	-0.02	-0.01
PCPs Rate	-0.04	0.03	0.02	-0.01	0.00	-0.02	-0.65	-0.72	-0.66	-0.66	-0.64	-0.57
Hospitals Per 100 Sq. Mi.	0.58	0.50	0.48	0.62	0.54	0.57	-0.58	-0.64	-0.60	-0.57	-0.59	-0.51

Gray indicates $p < 0.05$

All Rates Are Per 100,000

PLWHA = People Living with HIV/AIDS

PCP = Primary Care Physician

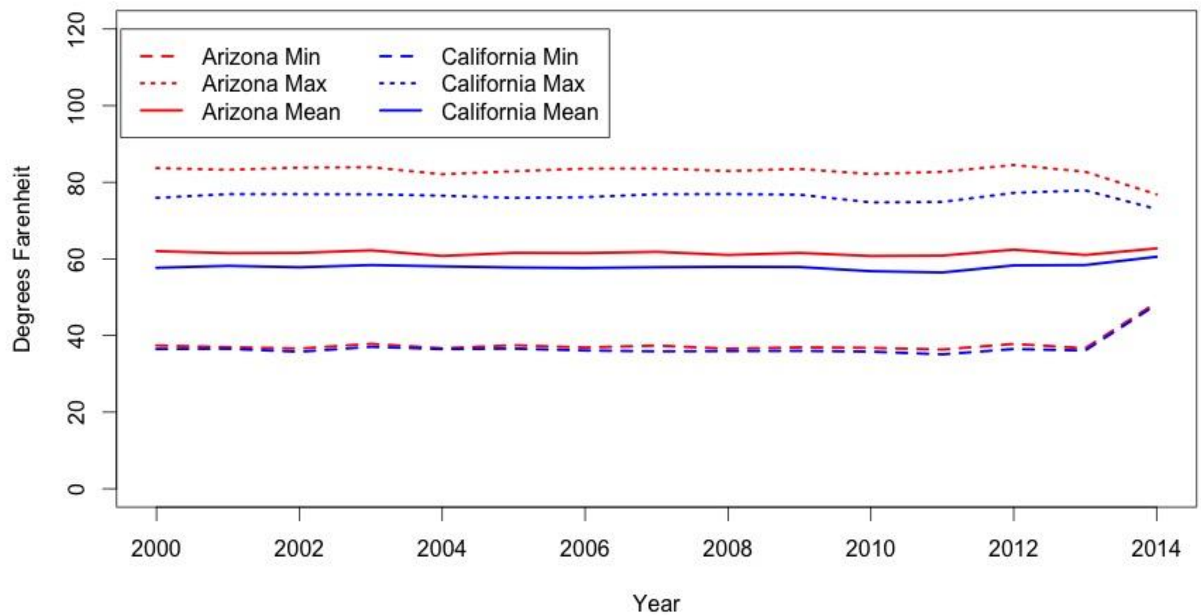

Figure 4: Inter-Annual Temperature. *Annual temperatures have remained consistent for both Arizona and California from 2000 to 2014.*

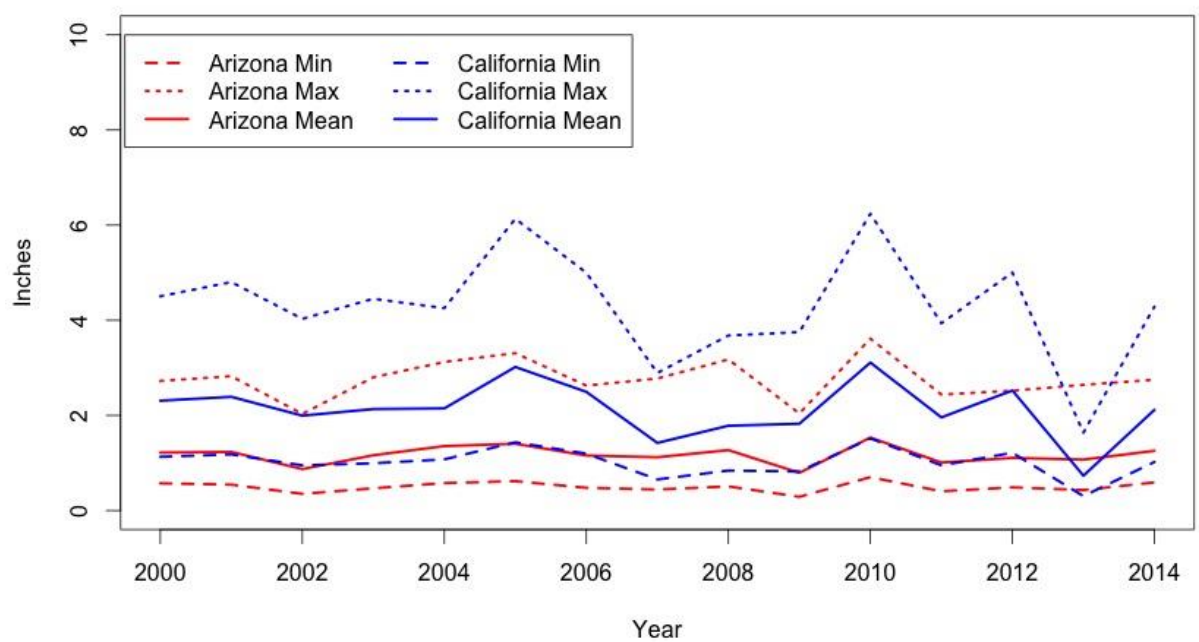

Figure 5: Inter-Annual Precipitation. *Annual precipitation has fluctuated considerably in both states from 2000 to 2014.*

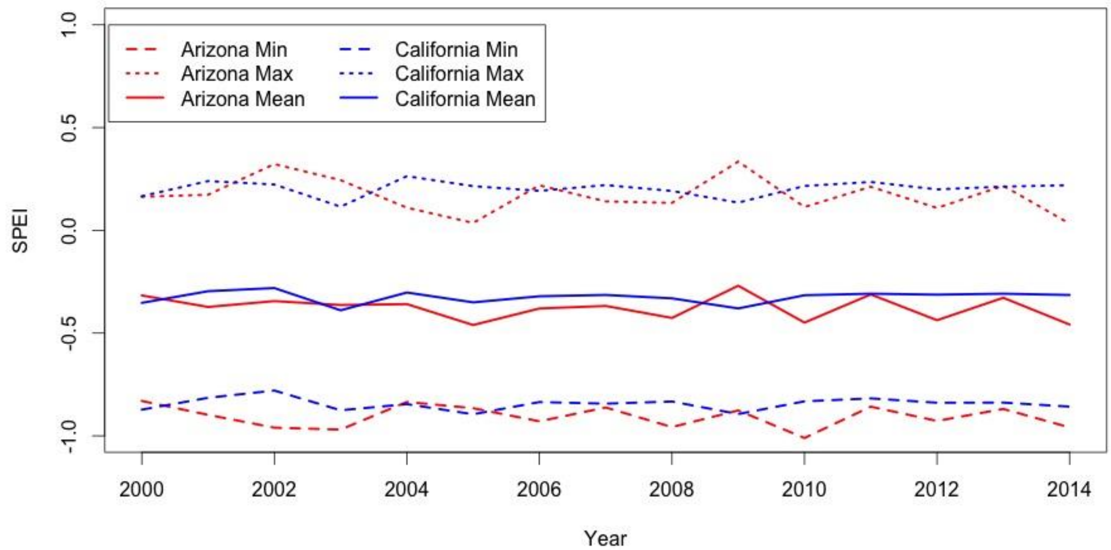

Figure 6: Inter-Annual SPEI. *Annual SPEI has undergone slight fluctuations in both states from 2000-2014.*

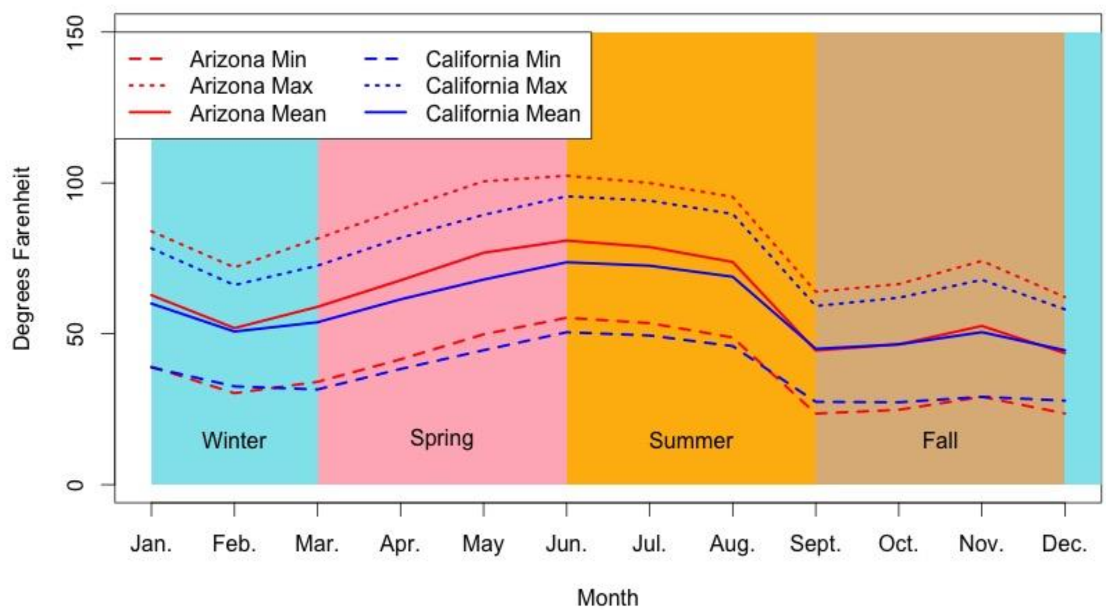

Figure 7: Intra-Annual Mean Temperature. *Mean temperature in both states peaks in the spring and summer months and is at its lowest during the winter months.*

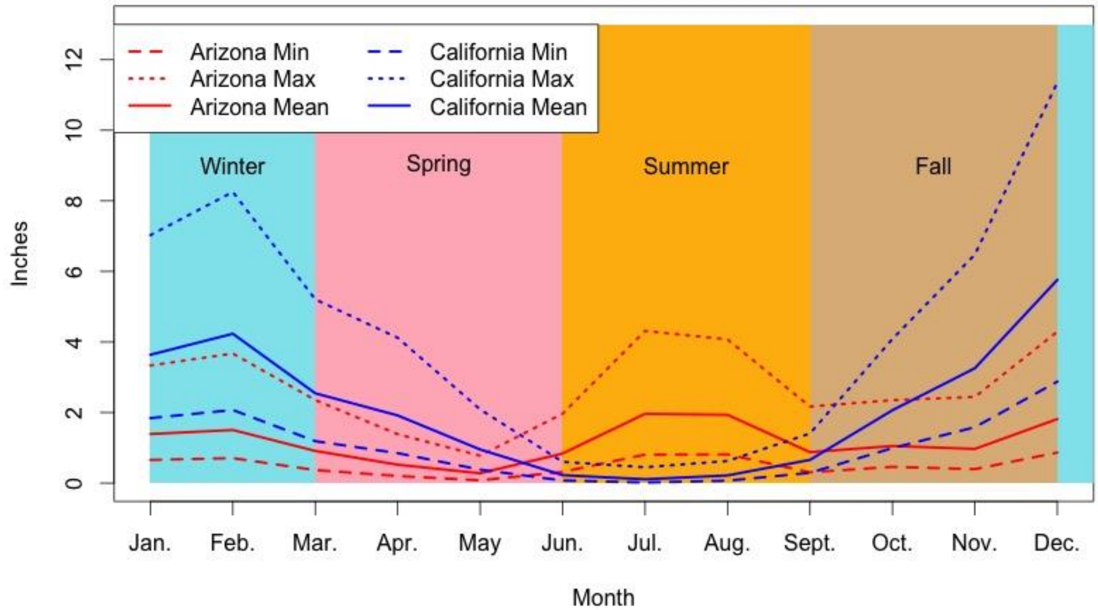

Figure 8: Intra-Annual Mean Precipitation. *Arizona's peak precipitation occurs in winter, while precipitation in California peaks in the winter and fall.*

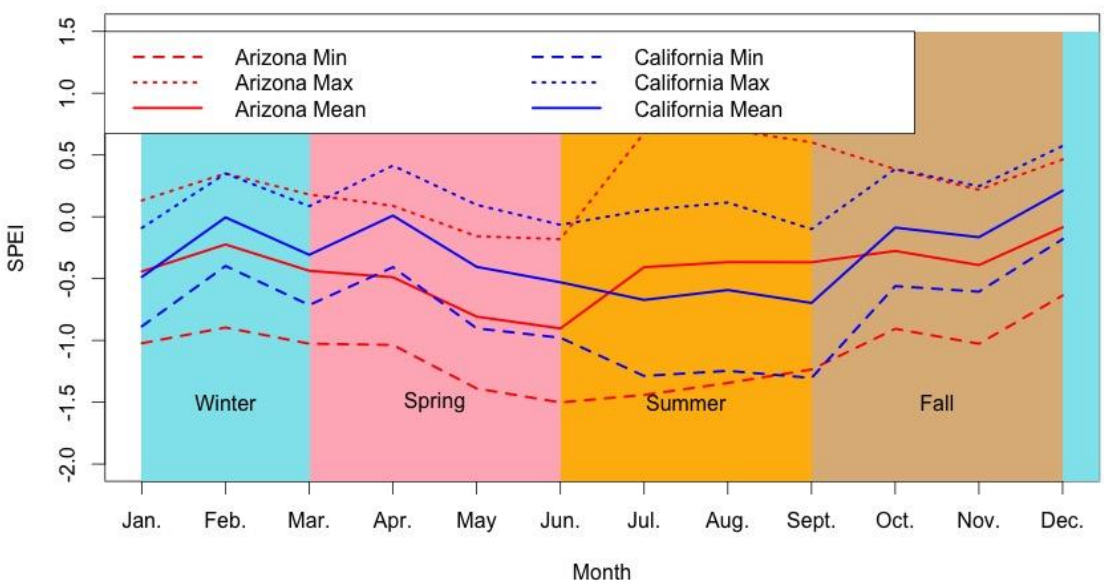

Figure 9: Intra-Annual Mean SPEI. *Arizona's mean SPEI tends to increase in the latter half of the year, while California's SPEI is generally higher at the beginning and end of the year.*

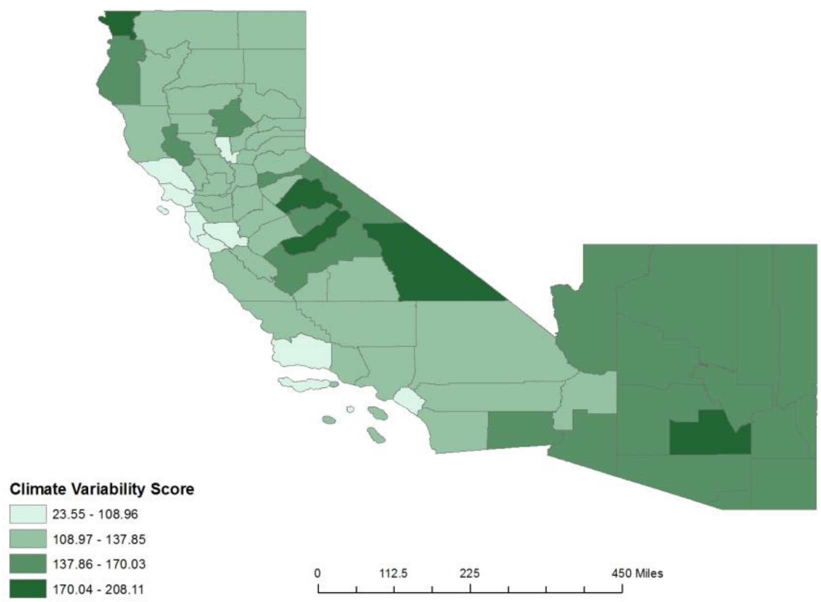

Figure 10: Overall Climate Variability Score. *Arizona counties generally had more overall climate variability than those in California.*

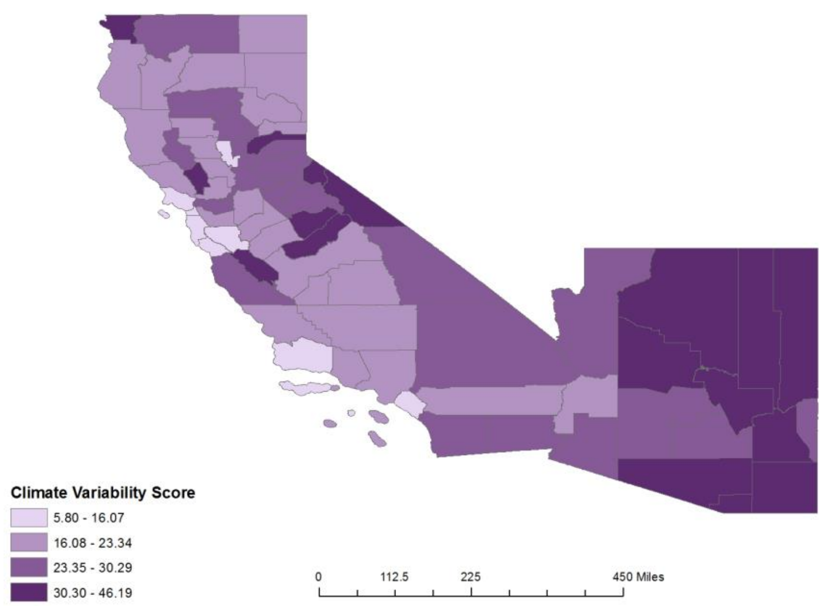

Figure 11: Spring Climate Variability Scores. *Arizona counties generally had more spring climate variability than those in California.*

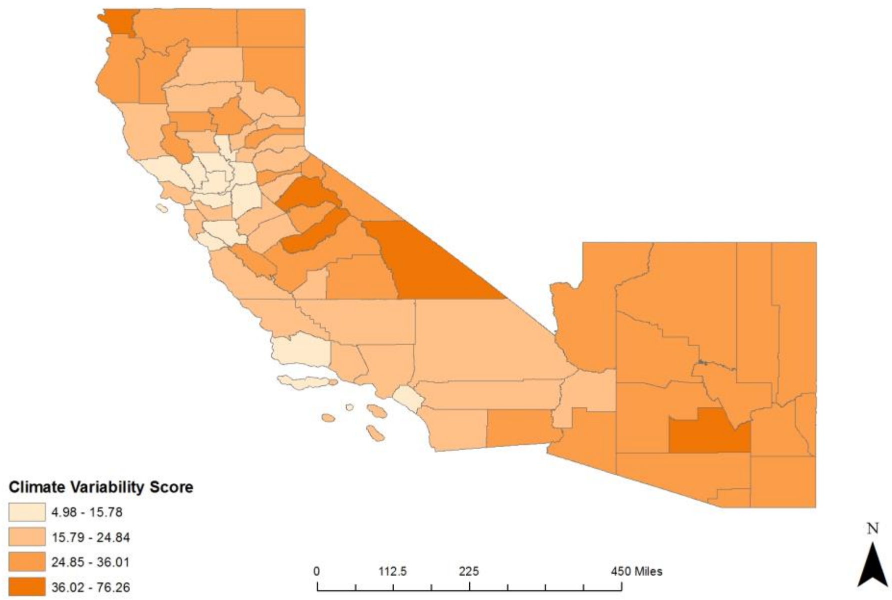

Figure 12. Summer Climate Variability Scores. *Arizona counties generally had more summer climate variability than those in California.*

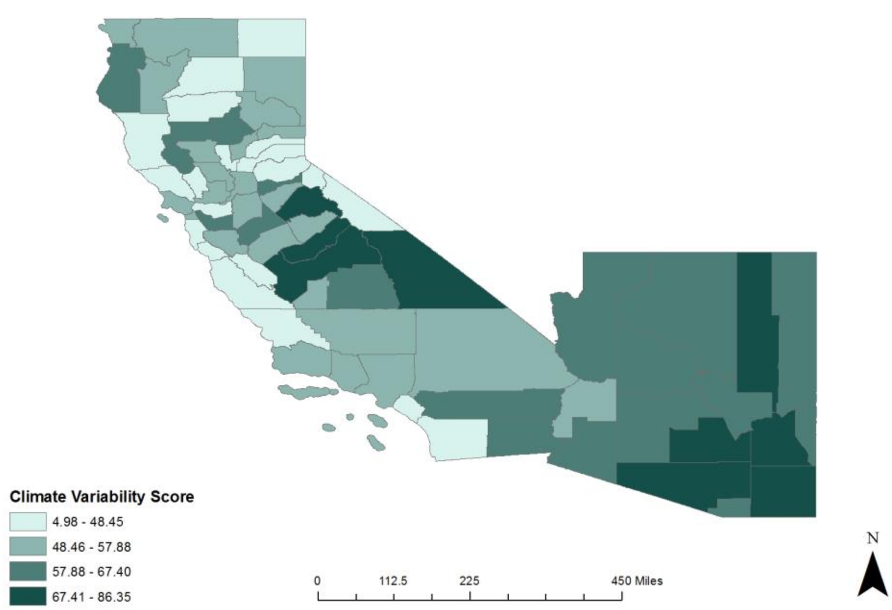

Figure 13. Fall Climate Variability Scores. *Arizona counties generally had more fall climate variability than those in California.*

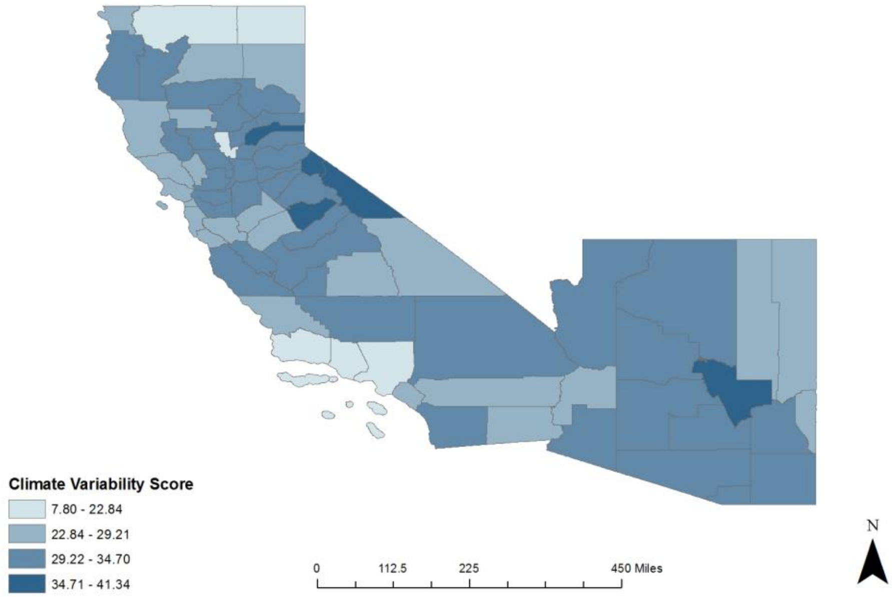

Figure 14: Winter Climate Variability Scores. *While levels of climate winter variability were less varied across states, Arizona counties generally had more climate variability than those in California.*

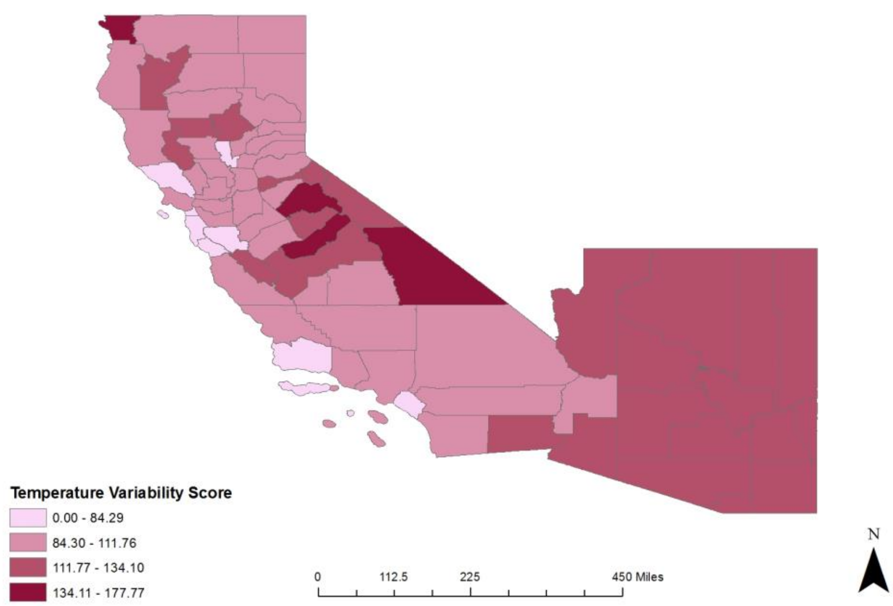

Figure 15: Overall Temperature Variability Scores. *While California contained the counties with the highest temperature variability, Arizona had higher average variability.*

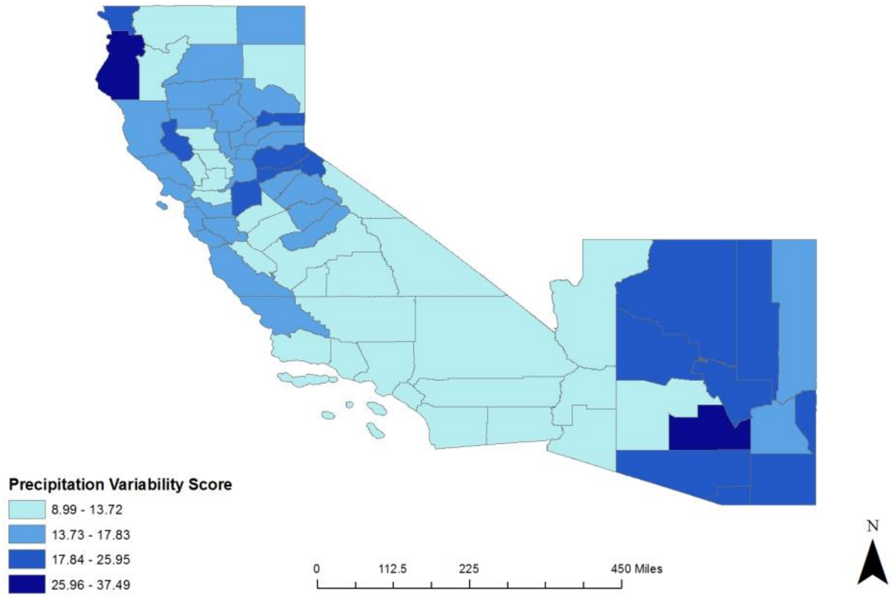

Figure 16: Overall Precipitation Variability Scores. *Arizona counties generally had more precipitation variability than those in California.*

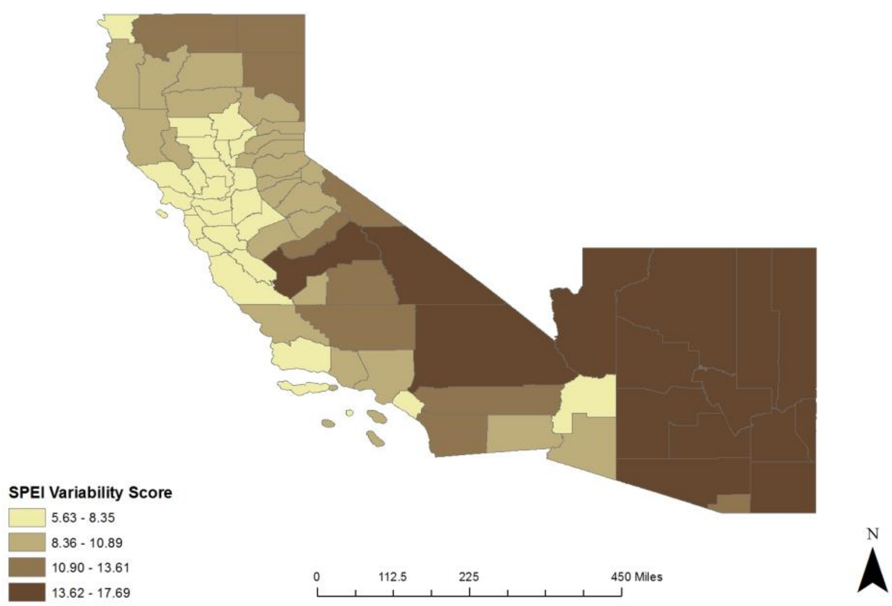

Figure 17: Overall SPEI Variability Scores. *Arizona counties generally had more SPEI variability than those in California.*

Table 4: Spearman Rank Correlation Coefficients for Vulnerability Indices and Coccidioidomycosis Incidence

		Mean Annual Incidence Rate	Mean 2010 Incidence Rate	Mean Fall Incidence Rate	Mean Spring Incidence Rate	Mean Summer Incidence Rate	Mean Winter Incidence Rate
Both States Combined	**Quartile Index**	0.15	0.18	0.14	0.14	0.10	0.12
	Percentile Index	0.22	0.24	0.21	0.21	0.19	0.19
	Modified Quartile Index	0.34	0.36	0.36	0.34	0.32	0.31
	Modified Percentile Index	0.36	0.37	0.37	0.35	0.33	0.33
Arizona Only	**Quartile Index**	-0.14	-0.11	-0.28	-0.17	-0.28	-0.05
	Percentile Index	0.04	0.07	-0.04	-0.01	-0.06	0.10
	Modified Quartile Index	0.43	0.39	0.36	0.41	0.34	0.47
	Modified Percentile Index	0.43	0.40	0.36	0.42	0.34	0.48
California Only	**Quartile Index**	0.44	0.47	0.48	0.43	0.37	0.32
	Percentile Index	0.46	0.50	0.50	0.46	0.42	0.36
	Modified Quartile Index	0.48	0.53	0.53	0.48	0.45	0.37
	Modified Percentile Index	0.52	0.57	0.57	0.54	0.48	0.42

Gray indicates $p < 0.05$

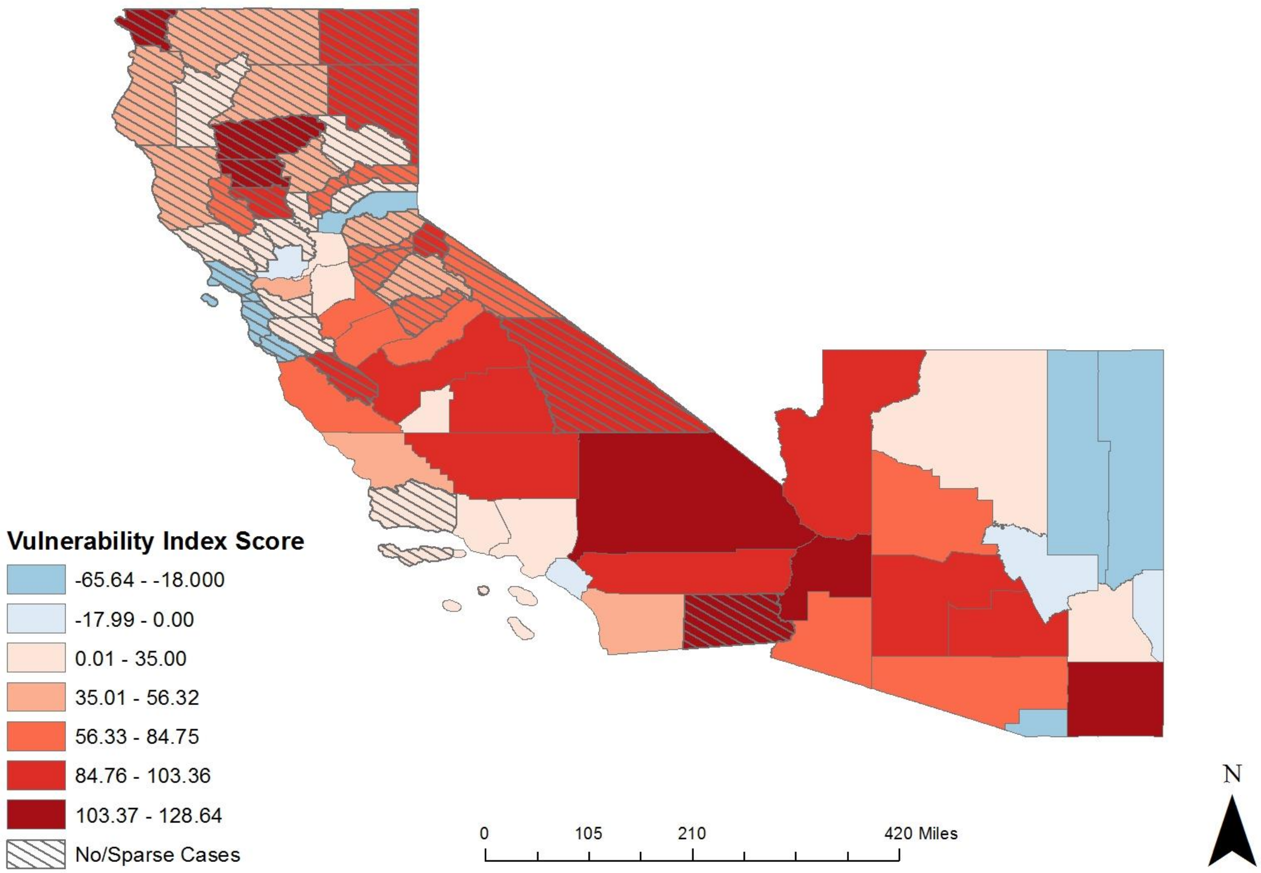

Figure 18: Coccidioidomycosis Vulnerability Index Scores. *Based on the index, the most vulnerable counties in the two states are Glenn County (CA), Cochise County (AZ), and Imperial County (CA). San Francisco County (CA), San Mateo County (CA), and Marin County (CA) are the least vulnerable to coccidioidomycosis.*

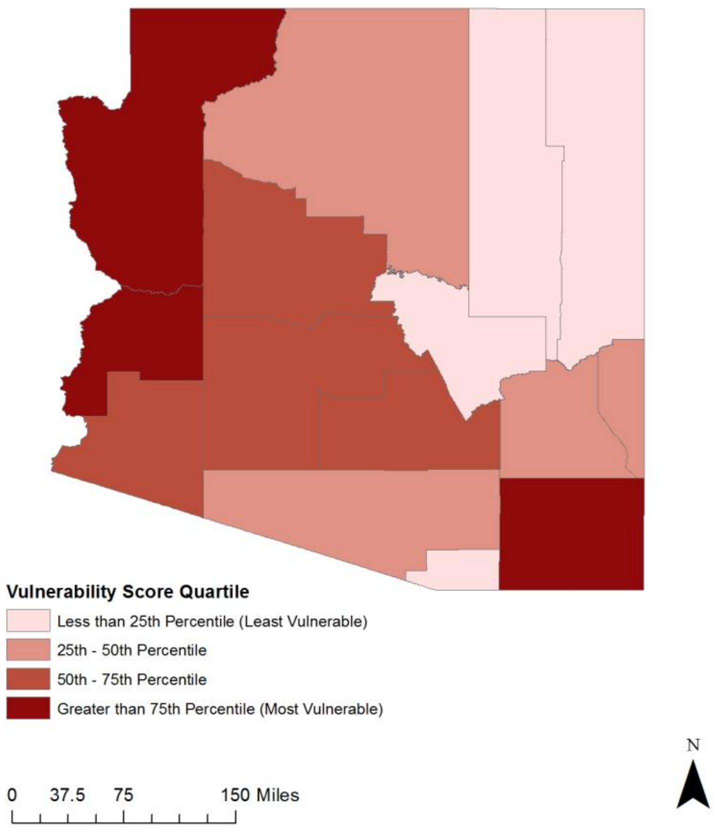

Figure 19: Arizona Coccidioidomycosis Vulnerability Score Quartiles. *Cochise and La Paz counties are most vulnerable, while Apache and Navajo counties are least vulnerable.*

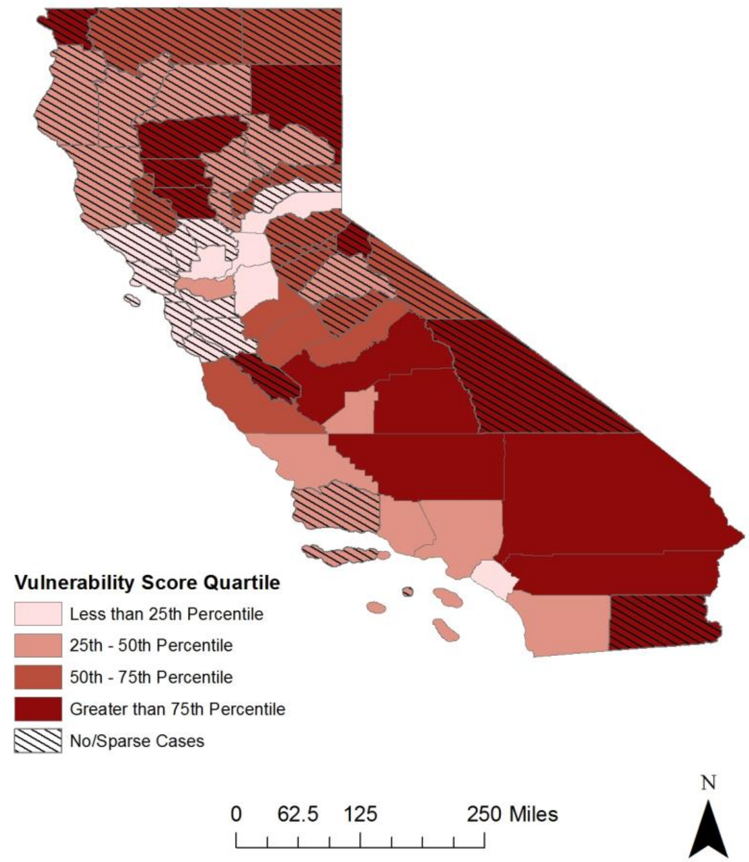

Figure 20: California Coccidioidomycosis Vulnerability Score Quartiles. *Glenn and Imperial counties are most vulnerable, while San Francisco and San Mateo counties are least vulnerable.*

Table 5: Spearman Rank Correlation Coefficients for Vulnerability Index Scores & Climate Variability Scores

	Both States	Arizona Index	California Index
Overall Variability	0.38	-0.14	0.65
Overall Precip. Variability	-0.27	-0.23	-0.22
Overall Temp. Variability	0.42	-0.05	0.64
Overall SPEI Variability	0.29	-0.41	0.56
Fall Variability	0.19	-0.19	0.35
Fall Precip. Variability	-0.26	-0.58	-0.23
Fall Temp. Variability	0.20	-0.05	0.33
Fall SPEI Variability	0.21	-0.34	0.43
Spring Variability	0.24	-0.64	0.48
Spring Precip. Variability	-0.26	-0.49	-0.21
Spring Temp. Variability	0.27	-0.66	0.49
Spring SPEI Variability	0.23	-0.50	0.46
Summer Variability	0.43	-0.15	0.65
Summer Precip. Variability	-0.01	-0.30	0.13
Summer Temp. Variability	0.53	0.03	0.64
Summer SPEI Variability	0.31	-0.35	0.58
Winter Variability	0.18	0.33	0.17
Winter Precip. Variability	-0.24	0.26	-0.36
Winter Temp. Variability	0.23	0.27	0.24
Winter SPEI Variability	-0.03	-0.02	0.04

Gray indicates $p < 0.05$

Appendix 2: CSTE Case Definition for Coccidioidomycosis [75]

Clinical Criteria

Infection may be asymptomatic or may produce an acute or chronic disease. Although the disease initially resembles an influenza-like or pneumonia-like febrile illness primarily involving the bronchopulmonary system, dissemination can occur to multiple organ systems. An illness is typically characterized by one or more of the following:

- Influenza-like signs and symptoms (e.g., fever, chest pain, cough, myalgia, arthralgia, and headache)
- Pneumonia or other pulmonary lesion, diagnosed by chest radiograph
- Erythema nodosum or erythema multiforme rash
- Involvement of bones, joints, or skin by dissemination
- Meningitis
- Involvement of viscera and lymph nodes

Laboratory Criteria

A confirmed case must meet at least one of the following laboratory criteria for diagnosis:

- Cultural, histopathologic, or molecular evidence of presence of *Coccidioides* species, OR
- Positive serologic test for coccidioidal antibodies in serum, cerebrospinal fluid, or other body fluids by:
    - Detection of coccidioidal immunoglobulin M (IgM) by immunodiffusion, enzyme immunoassay (EIA), latex agglutination, or tube precipitin, OR

- Detection of coccidioidal immunoglobulin G (IgG) by immunodiffusion, EIA, or complement fixation, OR
- Coccidioidal skin-test conversion from negative to positive after onset of clinical signs and symptoms

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