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Trends in coccidioidomycosis incidence in Arizona, 1998–2017:

Surveillance changes, weather, and land use

By

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Doctor of Philosophy

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Trends in coccidioidomycosis incidence in Arizona, 1998–2017: Surveillance changes, weather, and land use

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M.S.P.H., Johns Hopkins University, 2010

B.A., University of California, Berkeley, 2008

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An abstract of

A dissertation submitted to the Faculty of the

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Abstract

Trends in coccidioidomycosis incidence in Arizona, 1998–2017:
Surveillance changes, weather, and land use
By Mohammed Abdul Basit Khan

Coccidioidomycosis is an infectious disease caused by inhalation of spores from *Coccidioides* spp., soil-dwelling fungi endemic in deserts of the Americas. Two-thirds of all cases reported in the United States occur among people living in three counties in central and southern Arizona. Since mandatory laboratory reporting began in 1997, rates of reported disease have increased five-fold. This dissertation examined the impact of surveillance changes on trends in reported coccidioidomycosis and assessed relationships between weather, land use change, and disease incidence.

Reporting and testing changes associated with the *Coccidioides* enzyme immunoassay at a commercial laboratory caused marked changes in case counts and complicate the interpretation of trends. I estimated bias-adjusted incidence trends in three Arizona counties using probabilistic bias analysis. Bias parameters were estimated from surveillance data and a validation study. Bias-adjusted rates of reported coccidioidomycosis in these three counties were 25% to 47% lower than observed rates. The adjusted average annual percent change in incidence ranged from 5% to 8%.

Weather-related phenomena are thought to influence the growth of *Coccidioides* and dispersal of spores. I estimated associations between environmental factors (precipitation, air temperature, wind speed, airborne particulate concentration) and incidence and attempted to address methodological issues (changes in surveillance, temporal aggregation of case counts, heterogeneity among reported cases) arising in modeling these relationships. I found positive correlations between one- to two-year lagged winter precipitation, preceding average temperature, and monthly incidence rate. Results were consistent across crude and bias-adjusted analyses and did not change meaningfully using seasonal rates and cases aged 65 years and older.

Residential development in native desert has been hypothesized to increase incidence. I examined the relationship between land development and 2017 census tract incidence. Land development was measured as proportion of structures built after 2010 and remotely sensed development of native desert. Bayesian spatially varying coefficient models were used to estimate associations between land development and incidence. Greater land development was weakly associated (RR 1.04 95%, CrI: 1.01, 1.07) with higher incidence.

Collectively, these studies advance the epidemiology of coccidioidomycosis by more accurately estimating incidence trends and informing efforts by public health agencies to understand coccidioidomycosis risk.

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Most importantly, I want to thank my family. My gracious in-laws have been understanding and supportive throughout the lengthy course of this work. My wonderful sisters each guided me in unique ways, problem solving and listening to my frustrations with affection and much-needed humor. My parents have always supported and encouraged all of my educational endeavors; I would be lost without them. Finally, I thank my wife Nida for her steadfast love and support.

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CHAPTER 1: BACKGROUND

Biology of *Coccidioides*

Coccidioidomycosis, also known as Valley fever, is an infectious disease caused by *Coccidioides* ('resembling Coccidia') spp., soil-dwelling fungi endemic to parts of the Americas. *C. immitis* and *C. posadasii* cause human and animal infections.[1] These fungi have a complex life cycle and can switch between saprobic and parasitic phases (Figure 1-1).[2] The presumed saprobic stage is primarily found in the environment. During this stage, the fungi produce divided hyphae one to two microns in diameter, which become cylindrical two by five micron structures called arthroconidia.[3] These structures are separated by "empty, degenerate cells" that are easily disrupted and released into the environment.[3] Arthroconidia can spread the fungus in the environment and have slow settling rates, allowing them to remain airborne for long periods of time.[2]

The parasitic form occurs inside the host. Infection has been documented in many different animal species, ranging from sea mammals to primates.[3] Infection occurs upon inhalation of airborne arthroconidia. The minimum infectious dose is unknown, but as few as 10 arthroconidia can cause infection in laboratory mice. [3] The arthroconidia, in response to cues in the host milieu such as CO_2 levels and the activity of neutrophils, transforms into a larger multinucleate structure called a spherule.[3] Spherules internally subdivide and burst to release endospores, which can spread and infect surrounding tissue. The endospores grow into spherules, repeating the cycle of infection.[2]

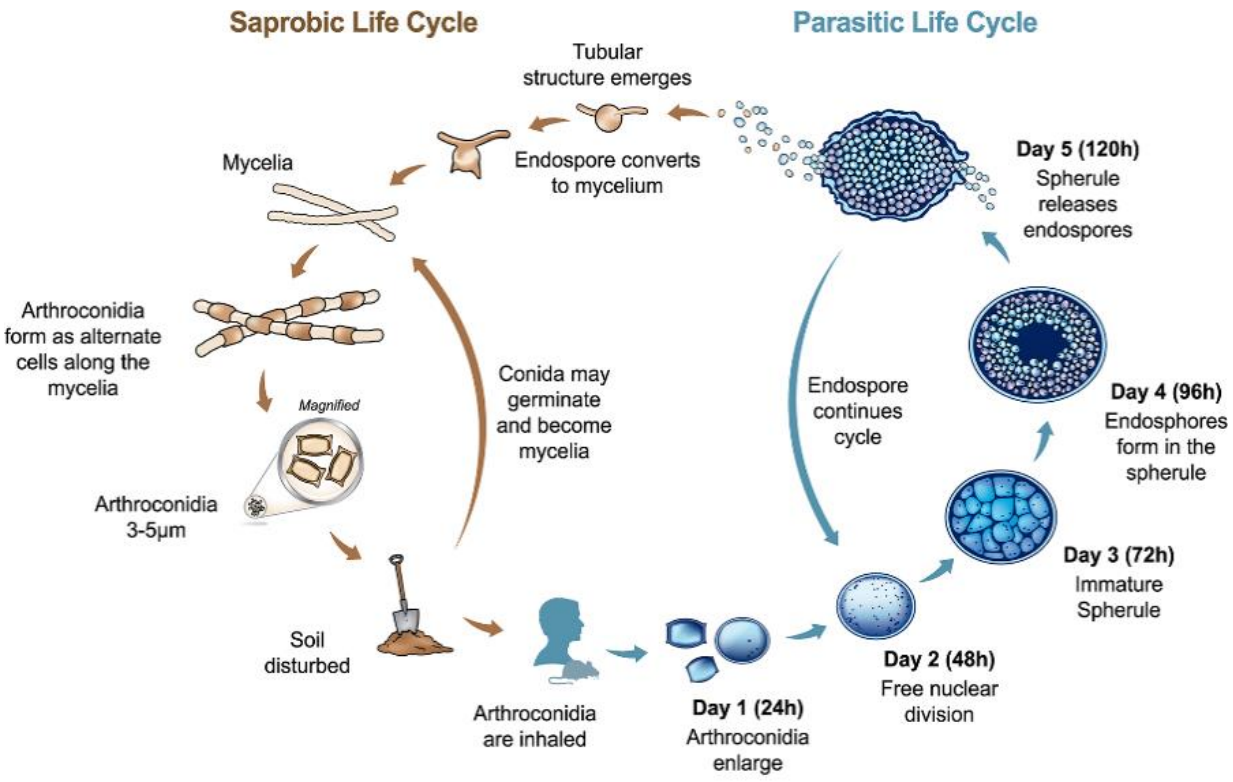


Figure 1-1. Life cycle of *Coccidioides*

Source: Lewis ERG, Bowers JR, Barker BM (2015) Dust Devil: The Life and Times of the Fungus That Causes Valley Fever. PLOS Pathogens 11(5): e1004762. https://doi.org/10.1371/journal.ppat.1004762. Licensed under Creative Commons (CC) Attribution 4.0 International License.

The range and ecological niche of *Coccidioides* in the environment is unclear. Range and endemicity have primarily been defined through detection of infections or evidence of immunity in humans and domestic and wild animals (Figure 1-2). *Coccidioides* are found in the top 10–30 cm of sandy, porous soil[4] in deserts characterized by hot summers, mild winters, and 10–50 cm of annual rainfall.[5] The distribution of fungi in soil appears to be highly focal with most soil samples testing negative.[6,7] Determinants of its distribution in soil are not well-understood. The fungus requires moist soil to grow. In dry conditions, hyphae desiccate and mature into

arthroconidia. The organism does not appear to thrive in cultivated soil (i.e., agricultural land), possibly due to increased competition with other microbes.[8]

Some authors have speculated that rodents are the primary hosts of *Coccidioides*, but definitive evidence is lacking.[9] Comparative genetic analysis of *Coccidioides* and related fungi noted expansions for gene families (e.g., keratin degradation and toxin production) linked to survival in mammals and loss of genes for decomposition of plant tissue, suggesting adaptation to infect mammals.[10] Soils near rodent burrows have tested positive for *Coccidioides*[2,11–13] and wild rodents have tested positive for infection.[12,14] *Coccidioides* has also been recovered in the soil after burial of infected animal tissues.[3]

In Arizona, most cases of coccidioidomycosis are thought to be caused by *C. posadasii*, whereas *C. immitis* predominates in California.[15] *C. posadasii* was only recognized as a separate species in 2002 based on genetic analyses; the species are indistinguishable without genetic testing.[16] *C. immitis* has been found in the San Joaquin Valley of California, Utah, and eastern Washington state, while *C. posadasii* has been found in Arizona, New Mexico, western Texas, northern Mexico, and parts of Central and South America.[2,17] Differences in temperature and salt tolerance between species have been documented, but systematic differences in virulence by species have not been observed.[2] However, strain-specific variation in virulence and immune response has been shown in the laboratory.[2] Morphological variation by strain and species has also been documented in cultures.[18] Genetic sequencing studies have also revealed a complex, diverse population structure and identified signs of sexual reproduction and hybridization between species through an unknown mechanism.[17,19] *C. posadasii* appears to be the older species.[17]

Genetic studies are limited by a lack of environmental samples: methods to isolate and genetically characterize strains in soil and air have only been developed recently. Past analyses relied upon clinical isolates obtained from humans and animals or soil passed through mice.[2] Most clinical isolates have a unique genotype.[20] Recent studies have detected airborne *Coccidioides* DNA using air sampling[21] and found variation[22] in estimated arthroconidia concentration by location and season in the Phoenix metropolitan area.

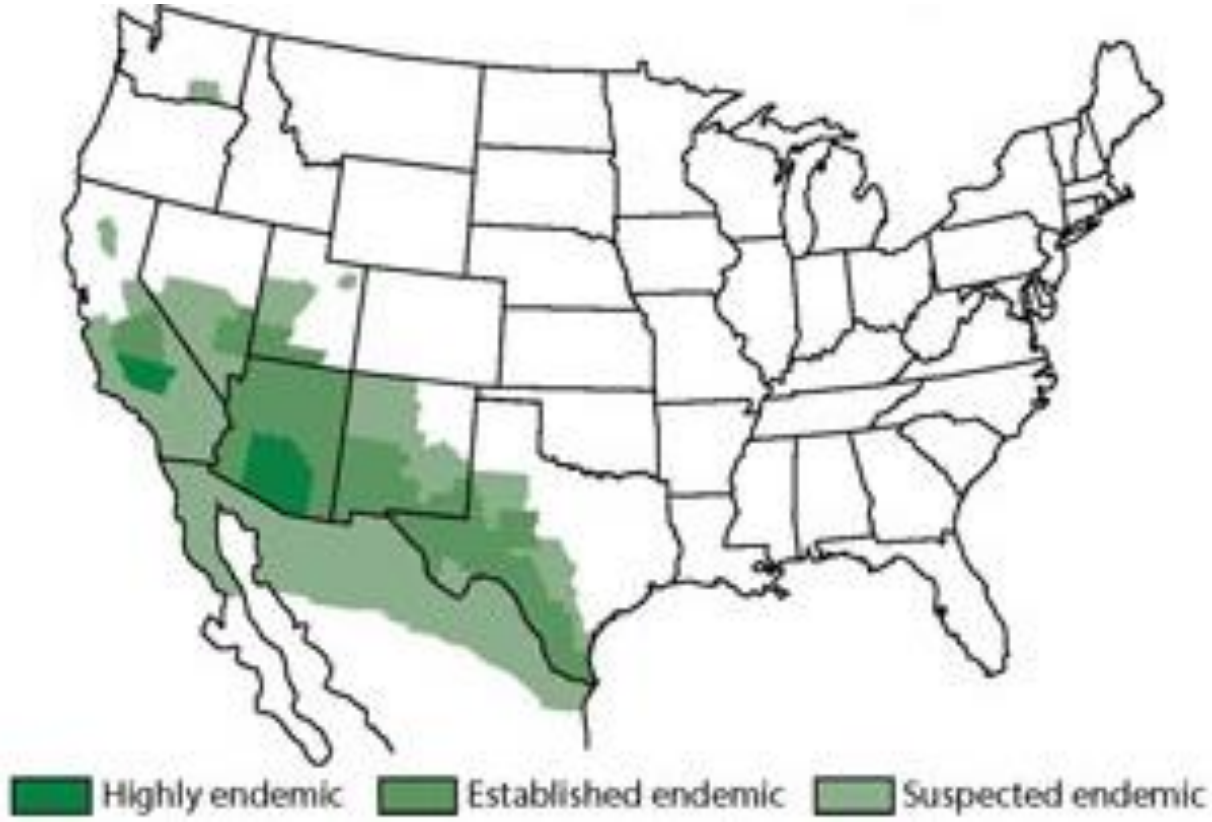


Figure 1-2. Areas endemic for coccidioidomycosis
Source: CDC[23]

Coccidioidomycosis in Humans

Clinical Course

Coccidioides were first found to infect humans by Alejandro Posadas, a medical intern who examined skin lesions in an Argentine soldier in Buenos Aires in 1892.[24] The pathogen was

initially thought to be a protozoan and assumed to cause lethal granulomatous disease. The first case in the United States was documented in California. Seminal studies of pathogenesis and epidemiology were conducted in the early twentieth century. A medical student at Stanford University was exposed to spores from a *Coccidioides* culture in the laboratory and became ill with pneumonia. His subsequent recovery and sputum culture suggested *Coccidioides* could cause non-lethal illness. Later studies in the 1930s and '40s established that, in addition to lethal, disseminated disease, *Coccidioides* caused San Joaquin Valley fever, a previously described syndrome, and that infection was associated with inhalation of dust.[24]

Much of our knowledge about the natural history of coccidioidomycosis comes from studies of U.S. military personnel in the San Joaquin Valley during World War II by Charles E. Smith et al.[25] Testing and examination of airmen revealed that 60% of infections were asymptomatic.[26] The remainder progress to respiratory illnesses with a broad spectrum ranging from influenza- or pneumonia-like febrile illness (symptoms include cough, chest pain, shortness of breath, night sweats, fatigue, arthralgias, myalgias, and rash, particularly erythema nodosum) and severe pneumonia to acute respiratory failure.[27] Smith et al. estimated that 25% of all infections were "clinically important" and severe enough to result in missing work.[25] The incubation period is estimated to be one to four weeks.[28] Most patients with acute primary pulmonary coccidioidomycosis recover without treatment within weeks or months.[29,30] However, even patients with mild disease may have fatigue or cough for up to six months.[31] Complications of pulmonary disease include pleural effusion and cavitary disease.[29,30] A small, unknown proportion of patients develop chronic pulmonary disease. Residual signs of infection (i.e., nodules, cavities) are frequently noted on chest radiography in recovered patients, even after asymptomatic infection.[27] Infection results in lasting immunity except when the cellular immune

response is already severely impaired (e.g., in AIDS patients or in organ transplant recipients).[32] Larger doses of arthroconidia may result in more severe respiratory illness.[33]

In less than one percent of infections, there is lymphatic or hematogenous spread to sites outside the thoracic cavity.[34] Dissemination generally occurs within months of infection, but infections years or even decades after exposure have been observed; preceding respiratory illness is often not noted or recalled.[26] Common sites of dissemination are the central nervous system, bones, joints, and skin, but infections have been documented in nearly all organ systems.[30] Impaired cellular immunity (e.g., due to HIV or immunosuppressive therapy, particularly for organ transplant), Black race, male sex, pregnancy, and possibly Filipino, Hispanic and American Indian race and ethnicity are risk factors for the spread of infection outside the thoracic cavity ('disseminated disease').[34] Other rare inherited immunogenetic defects have also been associated with severe disease.[35] Disseminated disease requires antifungal treatment, often prolonged. Coccidioidal meningitis is fatal without treatment and generally requires lifelong treatment.[36]

The immune response to coccidioidal infection is complex and not fully understood.[1,32] Early studies identified immune responses to tube precipitin (TP) antigen, composed of fungal cell wall polysaccharide, and complement fixation (CF) antigen, composed of fungal chitinase. Though weak cross-reactivity may occur, TP antigen predominantly reacts with immunoglobulin M (IgM) and CF antigen predominantly reacts with immunoglobulin G (IgG). TP antibodies develop earlier in illness than CF antibodies.[37] Ninety percent of patients with primary pulmonary coccidioidomycosis studied in the 1940s had detectable IgM antibody by week three of illness, and reactivity faded in 96% of patients by month seven.[37] IgG antibody appears later in the course of illness and can be quantitated and tracked to provide information about the

severity and course of infection. [37] Both IgM and IgG antibodies can reappear and persist in disseminated or chronic infections. [37] Cellular immunity develops in most immunocompetent patients. A T-cell response, especially Th1 and Th17 cells, is required for immunity to develop.[38] The role of humoral immunity is unclear.[39] Reinfections have not been documented. Reactivation of a latent infection is possible in patients who become severely immunosuppressed (e.g., due to AIDS and antirejection therapy for organ transplant recipients).[32] Attempts to develop a human vaccine have been unsuccessful to date, although candidates have successfully protected laboratory animals from infection.[38]

Diagnosis of coccidioidomycosis is rarely possible without laboratory testing, which may include culture, histopathology, polymerase chain reaction, dermal hypersensitivity test, and/or serology.[29] Culture or histopathologic evidence of infection is diagnostic. The skin test, recently re-introduced to the U.S. market, elicits a delayed-type hypersensitivity reaction in response to the injection of an antigen. A response is associated with the development of durable immunity.[37] Antigen-based tests are also available,[40] though not widely used.[30] Serological tests include enzyme immunoassay (EIA), tube precipitin, latex agglutination, quantitative and qualitative immunodiffusion, and complement fixation. Serological tests detect the host immune response to infection in body fluids such as serum and cerebrospinal fluid. Detection of antibodies may indicate current infection (symptomatic and asymptomatic) or past infection or may be falsely positive (e.g., due to cross-reactivity to histoplasmosis or other illness).[41] Antibodies can also be detected in cerebrospinal fluid and other body fluids.[37] Asymptomatic infections can be detected primarily via the skin test, though a small proportion (~7%) of patients may also be seropositive.[37] Infection cannot be ruled out by seronegative test results alone.[37]

EIA kits are likely more sensitive than immunodiffusion, complement fixation, and tube precipitin[37] and may detect antibodies earlier in infection.[42,43] Some commercial EIA kits use proprietary antigens. Immunodiffusion and complement fixation are more labor intensive and time-consuming, and require more technical expertise than EIA.[28,41] The EIA involves spectrophotometric readings to measure optical density and interpreting the values based on cutoffs provided by the manufacturers.[41] A result can be interpreted as positive, indeterminate, or negative. In some reference laboratories (e.g., 'Lab A'), specimens are first tested by EIA and then, if positive, tested by immunodiffusion and complement fixation.[44]

Epidemiology of Coccidioidomycosis in Arizona

The first case of coccidioidomycosis in Arizona was described in 1938.[45] In Arizona, coccidioidomycosis cases have been reported the Arizona Department of Health Services (ADHS) since the 1950's. It is one of the most frequently reported infectious diseases in Arizona, exceeded only by influenza, chlamydia, and gonorrhea. Approximately two-thirds of all nationally reported coccidioidomycosis cases between 1998 and 2017 occurred among Arizona residents.

Incidence

Estimating the incidence of coccidioidomycosis is challenging for several reasons. First, an unknown proportion of the population is immune due to previous infection with *Coccidioides* and is thus not at risk. It is also unknown whether this fraction has changed substantially over time. Second, surveillance changes, which are discussed in detail in Chapters 2 and 3, dramatically affected case counts and complicate the interpretation of trends. Case reports appear to have increased independently of surveillance changes as well. Finally, most infections are asymptomatic or mild, and patients with coccidioidomycosis may not seek care for their illness,

if any, and may not be tested for it.[46] Thus, the number of reported coccidioidomycosis cases underestimates the true number of incidence infections. The rate of reported disease also underestimates the true incidence rate because the entire population is assumed to be at risk. Contemporary prospective cohort studies of the risk of coccidioidomycosis in susceptible persons in endemic areas are lacking. Blair et al. estimated the one-year risk of infection in 210 healthcare system employees in 2012 and found that 11 (5%, 95% CI: 2%, 8%) had evidence of infection. Notably, this study used an in vitro lymphocyte-activation assay to measure cellular immunity to coccidioidomycosis to exclude immune persons and identify asymptomatic infection.[47]

Rates of reported disease in Arizona between 1990 and 2016 have ranged from 7 cases per 100,000 person-years (count: 191 cases) in 1990 to 248 cases per 100,000 person-years (count: 16,472 cases) in 2011. Surveillance changes, which are discussed in detail below, complicate the interpretation of trends. Case reports appear to have increased independently of surveillance changes as well. For example, rates increased between 2009 and 2012, when no documented surveillance changes occurred. The number of reported cases remained relatively constant in the 1980s (median case count 211 and range: 191 to 342).[48] Rates of reported disease in Arizona between 1990 and 2017 have ranged from 7 cases per 100,000 person-years (count: 191 cases) in 1990 to 248 cases per 100,000 person-years (count: 16,472 cases) in 2011. Between 1990 and 1995, the incidence rate increased from 7 per 100,000 person-years to 15 per 100,000 person-years.

Substantial interannual variability in reported incidence has been observed for decades. Annual epidemics of coccidioidomycosis have been reported in Arizona during the 1990s and 2000s.[49–51] The all-time highest number of case reports (16,472) was in 2011. In 2011,

coccidioidomycosis was the second most frequently reported notifiable disease in Arizona.[50] Overall, demographic characteristics of cases reported during epidemic years are similar to those occurring in other years. Epidemics have occasionally had seasonal patterns that differ from non-epidemic years. In 2011, the late summer and winter peaks were relatively diminished. In 2015, case counts peaked in September, months before the usual December/January seasonal peak.[45] Hospitalization and mortality counts and rates do not always appear to increase in tandem with epidemics.[50] Underreporting and miscoding of underlying causes of death and discharge diagnoses may explain this discrepancy. Four outbreaks of coccidioidomycosis in Arizona have been reported in the literature.[52] Three of these reports are from the 1940s. The most recent outbreak was reported in 1992. Four members of the same family developed coccidioidomycosis four days after digging a pit on the Salt River Pima Indian tribal reservation; two individuals required hospitalization.[53] All reported outbreaks occurred in central and southern Arizona. Given the limited data available on reported cases and the high background rate of disease, it is possible that point-source outbreaks go undetected.

Seasonality of reports has long been observed in cases reported to ADHS. Reports generally peak in December with a second peak sometimes observed in the late summer. Reports reach a nadir in the late spring. Exceptions to this pattern include cases reported in 2011, when little seasonality was observed, and 2015, whereas cases peaked in September. Coccidioidomycosis cases at the University of Arizona student health clinic in Tucson similarly had two annual peaks.[54] Coccidioidomycosis hospitalizations at Williams Air Force Base in Maricopa County from 1952 to 1956 peaked in July and in the fall (October/November).[55]

A large number of persons (often referred to as ‘snow birds’) visit Arizona during the winter months due to the temperate climate. These individuals are less likely to be immune to

infection as they often reside in areas where the disease is not endemic and are unlikely to have previously had coccidioidomycosis. Some of these individuals may have homes in Arizona and if they develop coccidioidomycosis, be reported as a resident case. Park et al. used home security data to estimate that there were 300,000 visitors between December and March annually between 1998 and 2001. They found that removing these individuals from the denominator did not meaningfully affect the seasonal pattern of incidence rates.

Prevalence

The prevalence of coccidioidomycosis in Arizona is difficult to estimate since the infection is most often asymptomatic or mild. Several studies have estimated the prevalence of immunity (i.e., skin test reactivity) or antibodies. Most of these studies were conducted in the mid-twentieth century. Skin testing studies are complicated by the use of differing or non-standardized antigens (e.g., coccidioidin vs. spherulin) and cross-reactivity with previous exposure to histoplasmosis.[56] Edwards and Palmer generated national county-specific estimates of the prevalence of skin test reactivity, which are the basis of the relative endemicity map in Figure 1-2. The sample consisted of U.S. Navy recruits at the San Diego Naval Training Center, students at universities in the Great Lakes region, and female nursing students in 10 U.S. cities. Subjects were tested between 1949 and 1951. Each subject provided a lifetime residential history at the time of testing. Prevalence estimates were calculated based on 48,676 White subjects aged 17–21 years (80% male Naval recruits) who had spent their entire lives in one county. Note that many Arizona counties had not been established at the time this study was conducted. Prevalence estimates were only published by category and ranged from 10–30% in the northern and westerns parts of the state to 50–70% in central and southern Arizona.[57]

In 1951, Emmet et al. skin tested 1,869 school children from schools in Phoenix with coccidioidin and found that 794 (42%) had positive results. Percent reactivity increased with age, ranging from 26% in 5–6 year old students and 60% in 11–12 year old students; there was no meaningful difference in reactivity between 11–12 year, 13–14, and 15–16 year old age groups. Reactivity did not differ by sex. All children with positive results and 228 students with negative results received chest x-rays; 13% and 14% had evidence of pulmonary calcification.[58]A subsequent study of 955 lifetime Arizona resident high school and college students found that 568 (59%) were reactive to the skin test, with variation by race (higher prevalence among non-Whites) and county of origin (higher prevalence in southern and central counties).[59]

In 1961, 8,401 children from 32 elementary and high schools in Maricopa County were tested with coccidioidin. Of these, 7,982 (95%) lived at least 80% of their lives in Maricopa County. Overall, 32% had positive skin test results. Children who were lifetime residents had were more likely to be reactive (37%) compared to non-lifetime residents (28%). Among lifetime residents, prevalence of immunity was 20% among five-year old students and 65% among 18-year old students. Prevalence did not vary by sex. There was large variation in reactivity by school (range: 19–83% in elementary schools and 46–84% in high schools among lifetime residents). There was no difference in reactivity by sex. However, reactivity varied by race as follows: American Indians had the highest percentage, followed by Hispanic, Black, and White. Subjects with reactivity to histoplasmin generally had larger diameter reactions due to coccidioidin, suggesting limited cross-reactivity.[60]

Dodge et al. conducted a skin testing survey of a stratified random sample of White households in Tucson between 1977 and 1979. All persons over three years old were tested with two antigens coccidioidin and spherulin. Subjects measured their own induration, and a “spot

comparison" of nurse and subjects' readings found good agreement. Among 1,639 tested subjects with results, 30–33% had a positive test result. Patients with a self-reported history of disease were much more likely to be reactive (57% vs. 27%) than patients with no history. Patients with a self-reported history of disease and an abnormal chest x-ray. Reactivity was highest in subjects aged 15 to 64 years (39–44%), followed by subjects under 15 (30–37%), and subjects over 54 years old (19–21%). Males had a slightly higher prevalence than females (30–35% vs. 29–32%). "Exposure history" was assessed as a weighted of time lived in Arizona, California, or areas of lesser endemicity; subjects who lived for longer periods of time in Arizona or California had a higher prevalence of reactivity.[61] Six years prior, these subjects were interviewed and 10% reported a history of coccidioidomycosis.[62]

Tabor et al. conducted an address-based telephone survey in Tucson between 2002 and 2003 and estimated that one-percent of residents had a self-reported history of physician diagnosed-coccidioidomycosis within the past ten years and symptom onset at the current residence. Twelve-percent had a household history of coccidioidomycosis. The validity of self-report is unknown and not assessed by this study.[63] In a follow-up analysis, the authors estimated a 1992–2003 period prevalence of 88 per 100,000 population, compared with 34 reported cases per 100,000 population.[64]

Population-based seroprevalence studies have not been conducted. In the abovementioned study of healthcare employees by Blair et al., 12% (95% CI: 9%, 16%) had evidence of immunity.[47] In a study of EIA test kit specificity using sera from healthy blood bank donors in Arizona (n=1,218), 5–7% were reactive to EIA IgM, IgG, or both and 3–4% were EIA IgG reactive alone, which is associated with recent or past infection.[41]

Spatial Distribution

Though cases are reported from all 15 counties in Arizona, 95% of these cases occur among residents in Maricopa, Pima, and Pinal counties, where 80% of the state's population resides. Rates of reported disease are also highest in these areas. It is unclear why rates are lower in some southern counties (e.g., Yuma County), where climate and elevation does not differ significantly from Maricopa, Pima, and Pinal counties. Nonetheless, all areas of the state are assumed to be endemic. Edwards and Palmer generated nationwide county-specific estimates of the prevalence of skin test reactivity as discussed above.[57] Prevalence estimates were only published by category and ranged from 10–30% in the northern and westerns parts of the state to 50–70% in central and southern Arizona.[57]

The spatial distribution of disease at sub-county scales is understudied and important as counties in Arizona are very large. In a skin testing survey of school children in Maricopa County, reactivity prevalence varied most by location of school; schools in the same area of the county had similar prevalence estimates. Urban schools had a lower prevalence (20%) than suburban (45%), and rural (53–63%) schools. Reactivity varied by area with only 10–12% of children 5–8 years old reactive in Central Phoenix.[60] A study of reported cases between 1998 and 2001 found that the highest age-adjusted ZIP code-level rates in Maricopa County were in the periphery of the Phoenix metropolitan area.[65] More recently, age-adjusted spatial scan statistic analysis of 2013–2015 reported cases in Maricopa, Pima, and Pinal counties identified three clusters of higher than expected incidence (rate ratio range: 1.22, 1.65) and two clusters of lower than expected incidence (rate ratio range: 0.68, 0.73).[66]

In 2007, ADHS requested assistance from the CDC to investigate two-fold higher age-adjusted incidence of reported cases in the northwest Phoenix metropolitan area. The subsequent investigation attributed this increase to greater testing and disease awareness. Healthcare

providers in this area were more likely to attend coccidioidomycosis-specific continuing medical education and provide counseling to their patients. Reported cases living in this area were more likely to be tested earlier after symptom onset and with fewer reported symptoms. Tests ordered at a major reference laboratory were no more likely to be positive among patients living in this area compared with all other patients. Similarly, testing of remnant sera from a sample of patients living in this area and a comparison group from the rest of the metropolitan area found no difference in seropositivity. Finally, home security data revealed that approximately 20% of the population in this area were non-residents, perhaps inflating the numerator of the calculated incidence rate.[67]

Brown et al. examined the association between several areal characteristics and incidence for 2006–2009 cases in Arizona at the case residence, block group, tract, and ZIP code scales. Factors associated with incidence across scales included population over 65 (positively), median income (positively), soil organic carbon (negatively), medium and high density residential land (positively), pasture/hay land (negatively), and distance to desert (negatively). Associations with shrub/scrub land, cultivated crops, and distance to wetland varied in magnitude and/or direction by spatial scale.[68]

Risk factors for infection are not well understood. Identifying persons at risk for infection is difficult because establishing immunity requires skin testing, which is not currently licensed for use in asymptomatic patients and has unknown performance in this population. Patients with mild or asymptomatic infection are also difficult to enroll because they are unlikely to be seek care and be tested using the skin test or the serologic tests mentioned above. Thus, studies have mainly identified factors associated with increased risk of symptomatic or severe coccidioidomycosis.

Demographics

Rates of reported coccidioidomycosis in Arizona vary substantially by demographic characteristics such age, sex, and location of residence. The rate of reported disease increases with age, with the highest rate occurring among adults 70 years and older.[45] The age distribution of reported cases has changed over time.[69] Some changes in mean age were temporally associated with surveillance changes (e.g., decline in 2009 and increase in 2012), but median age declined independently of surveillance changes as well.[70] Older adults may be at higher risk of infection, may experience more severe disease, or may be more likely to seek care and be tested. However, a study comparing manifestations of disease between older and younger patients found no significant differences in clinical presentation after controlling for immunosuppression.[71] Age-specific rates also vary over time: with minor exceptions (1998–2001), rates have increased most among older age groups.[65]

The relationship between sex and risk of pulmonary coccidioidomycosis is unclear. In Arizona, the sex distribution of cases has changed over time. Between 1998 and 2008, 56% of reported cases were male. However, 55% of cases were female between 2009 and 2012.[50] This change corresponds with one of the surveillance changes discussed in detail in Chapter 2. It is unknown whether the risk of infection varies by race or ethnicity in Arizona. Race and ethnicity are not routinely recorded (<30% of cases) in coccidioidomycosis case reports in Arizona. A population-based survey of Pima County residents found that participants who self-reported a history of coccidioidomycosis were more likely to be non-Hispanic Black (OR: 2.7).[63] Several studies have found increased risk of severe or disseminated disease among Black, Hispanic, and American Indian patients. Seitz et al. estimated that the rate of hospitalization for disseminated coccidioidomycosis in Arizona was 12-fold higher among Black persons and 21-fold higher

among Hispanic persons as compared with White persons. This finding persisted when patients with ICD diagnosis codes for HIV or primary immune deficiency were excluded.[72] Studies have also documented higher rates of severe disease among American Indian populations in Arizona.[73] Few studies have examined the relationship between socioeconomic status and coccidioidomycosis. In the survey of Pima County residents, participants who reported a history of coccidioidomycosis had higher educational attainment than persons who did not: compared to respondents with a high school diploma, the odds of not having a high school diploma were 0.45 (95% CI: 0.21, 0.97) lower among cases than controls.[63]

Comorbidities

Reported coccidioidomycosis cases have a higher prevalence of comorbidities than the general population. For some conditions (e.g., HIV infection), this likely reflects decreased immune function and increased risk of severe illness, while other comorbidities (e.g., congestive heart failure) may be associated with greater care seeking and testing in comorbid patients. Smoking, congestive heart failure, cancer, and corticosteroid therapy were associated with case status in a 1996–1997 case-control study of symptomatic coccidioidomycosis among Arizona adults over 60 years age, although confidence intervals were extremely wide.[74] Twenty percent of 2007–2008 reported cases interviewed as part of enhanced surveillance were immunocompromised at the time of illness and two-thirds had an underlying condition.[75] Reported cases also have an elevated rate of all-cause mortality and hospitalization in the year following illness (unpublished analysis by the author).

Several underlying conditions are associated with severe or disseminated disease. Disseminated coccidioidomycosis is an AIDS-defining condition,[76] and people living with HIV infection are at risk for severe disease. However, risk varies by CD4 T-lymphocyte count, which

is consistent with the importance of cell-mediated immunity for control of this infection, and thus, viral suppression status. A study of 170 patients prior to the advent of highly-active antiretroviral therapy (HAART) estimated that 25% became ill with coccidioidomycosis during an average of 11 months of follow-up; AIDS diagnosis and CD4 count <250 cells/μL were associated with disease.[77] However, later studies conducted when HAART was available found substantially lower incidence.[78] Sunenshine et al. matched surveillance databases for HIV and coccidioidomycosis cases reported between 1992 and 2005. Of 23,704 coccidioidomycosis cases reported during the study period, 986 (4%) had HIV infection. However, among male cases less than fifty years old, the prevalence was 13%. They further estimated that 24% of deaths related to coccidioidomycosis occurred among patients with HIV infection.[79]

Iatrogenic immunosuppression is also a risk for severe disease. Risk likely varies by duration and intensity of therapy. Case series and small cohort studies from transplant programs in Arizona suggest that the risks of disease (5%–9% per year), dissemination, and death are high among solid organ transplant recipients. Patients are screened for infection and receive antifungal prophylaxis prior to induction based on a hypothesized risk of reactivation of previous infection. Contemporary protocols appear to have eliminated this risk, although further study is required. Findings among hematopoietic stem cell transplant recipients are similar. Another recently emerged risk factor for severe disease is biologic response modifying therapy. Several agents, particularly TNF-α inhibitors, appear to be associated with increased risk of infection and severe disease, although few studies have systematically evaluated this risk.[78]

Few studies have examined coccidioidomycosis among pregnant women in Arizona. Wack et al. reviewed medical records for women aged 15–45 years who had a positive *Coccidioides* laboratory result or an ICD-9 code for coccidioidomycosis as a discharge diagnosis

at three healthcare facilities in Tucson in the early 1980s. Among 47,120 pregnancies, ten cases of coccidioidomycosis were identified, four of whom had a clinical diagnosis of coccidioidomycosis.[80]

Migration

Relocation from a non-endemic area and time spent in an endemic area are associated with increased risk of infection. In a case-control study of coccidioidomycosis in adults 60+ years old, the median duration of residence in Arizona was 6.5 and 19.5 years among cases and controls, respectively. Twenty-five percent of cases were not full-time Arizona residents. Time lived in Arizona was inversely associated with risk of coccidioidomycosis as follows: <4 years OR 7.6 (95% CI: 2.8, 20.8); 4 – 12 years OR 4.7 (95% CI: 1.9, 11.5); 13 – 25 years OR 2.7 (95% CI: 1.1, 7.0). Risk declined approximately 5% per year lived in the state.[74] Ten- to fourteen-percent of interviewed cases reported 1998 and 2001 had lived in Arizona for less than one year.[65] In the 2007–2008 enhanced surveillance study, reported coccidioidomycosis cases had lived in Arizona for a median of 12 years while Arizona Behavioral Risk Factor Surveillance System (BRFSS) respondents had lived in Arizona for a median of 22 years.[75]

Activities

Several occupational outbreaks of coccidioidomycosis have been reported in California, but none have been reported in Arizona. Most of these outbreaks have been in low- to moderate-incidence counties as opposed to the endemic epicenters in the Central Valley.[81] Coccidioidomycosis is recognized as part of workers' compensation in California, but not in Arizona.[82] Enhanced surveillance investigations have found that 'white collar' workers were disproportionately represented among reported cases, although this may be explained by selection bias or access to care (unpublished). Many cases also report being retired.[48]

Although high-quality studies are lacking, studies have reported mixed findings regarding an elevated risk of infection associated with activities involving exposure to or generation of airborne dust. In an interview study of 300 coccidioidomycosis cases in Maricopa County, 15% of cases who worked outside reported engaging in soil disturbing activity; 14% of cases reported no outdoor activities.[83] A longitudinal study of seroconversion among healthcare workers found that regular outdoor recreational walking was associated with an increased risk of infection.[47] The rates of coccidioidomycosis between 1998 and 2006 were 374 cases per 100,000 person-year (95% CI: 192, 639) among scholarship athletes at the University of Arizona as compared with 90 cases per 100,000 person-year (95% CI: 79, 103) students seen at the student health center. However, this may be related to time spent outdoors, care seeking (e.g., due to declines in athletic performance) or recent migration to Arizona.[84]

Clinical Characteristics of Reported Cases

Population-based data on the characteristics of reported cases are limited. Data are derived from enhanced surveillance studies conducted by the state or county health departments and single- or multi-center studies of patients seen at a specific facility or health system. An interview study of 493 cases reported in 2007–2008 noted a significant burden of disease among reported cases. Most patients were still symptomatic at interview, but among those who had recovered, the median duration of symptoms was 42 days. Commonly reported symptoms included fatigue (84%), cough (67%), dyspnea (59%), and fever (54%). Delays in diagnosis were common: the median time between seeking care and diagnosis was 23 days. Among employed patients, 74% missed work and a median of 14 days were missed due to work. Similarly, 75% of patients were unable to perform activities of daily living while ill for a median of 47 days. Emergency room visits and hospitalization were common (46% and 41%, respectively). Sixty

percent of patients received at least one course of antibiotics, and 61% were prescribed antifungal medication. Given that only 58% of contacted cases were interviewed, selection bias is possible, and this sample may have been skewed towards severely ill patients.[75] Previous studies of reported cases have also found a substantial delay between symptom onset and diagnosis, long duration of symptoms, and high frequency of antibiotic prescription, antifungal treatment, and hospitalization.[65,85,86]

Donovan et al. assessed diagnostic delays among 276 coccidioidomycosis cases seen at a tertiary care center in Tucson. The median time between initial healthcare encounter and diagnosis was 23 days with 43% of patients having delays of one month or greater. Interestingly, diagnostic delays did not differ by disease type (acute pulmonary, chronic pulmonary, asymptomatic nodule, and disseminated infection).[87]

Hospitalization

ADHS also conducts surveillance for hospitalizations with a primary discharge diagnosis of coccidioidomycosis among Arizona residents at non-federal healthcare facilities. Annual hospitalization counts between 2003 and 2012 ranged from 800 to 1,070 hospitalizations. Pinal County had the highest rate of hospitalizations in the state. Hospitalized patients were predominantly male with a median age of 52 years. The median length of stay was four days. Primary pulmonary coccidioidomycosis was the most common discharge diagnosis (68%). Approximately 40% of hospitalizations involved intensive care. Between 2003 and 2012, charges for hospitalizations with a primary diagnosis of coccidioidomycosis totaled $636 million (2012 dollars). Medicare and Medicaid (the Arizona Healthcare Cost Containment System) were the most common expected sources of payment.[88]

Disseminated Disease

As coccidioidomycosis case reports lack clinical information, population-based data on the burden of disseminated disease are scant. Foley et al. requested medical records for all cases interviewed as part of 2007–2008 enhanced surveillance study. Records were received for 65% of patients, and of these, 26 (8%) had evidence of disseminated disease. Patients with disseminated disease were more likely to be male and Black, and have HIV infection. They were also more likely to require hospitalization and had a longer duration of symptoms.[89]
Between 2000 and 2009, the average annual incidence rate of hospitalization associated with disseminated coccidioidomycosis was 4.8 per 100,000 person-years. Seitz et al. estimated that the rate of hospitalization for disseminated coccidioidomycosis in Arizona was 12-fold higher among African Americans and 21-fold higher among Hispanics as compared with Whites. This finding persisted when patients with diagnosis codes for HIV or primary immune deficiency were excluded.[72]

Coccidioidal meningitis is a particularly severe form of dissemination. Between 2008 and 2014, 623 patients were hospitalized with diagnosis codes for coccidioidal meningitis in Arizona. Readmission rates were particularly high in this group of patients: 35% of patients were readmitted at least once during the study period with a median time to readmission of 83 days. Sixty-one percent of these patients were admitted to the intensive care unit. Diabetes (23%) and HIV (20%) were frequently recorded underlying conditions. Admitting diagnoses also reflected severe complications of infection such as obstructive hydrocephalus.[90]

Death

Death due to coccidioidomycosis is rare. Between 1990 and 2008, 1,010 decedents in Arizona had a cause of death code for coccidioidomycosis, an average age-adjusted mortality rate of 2.2 per 100,000 person-years.[91] Age and male sex (OR: 1.76, 95% CI: 1.38, 2.26) were

associated with coccidioidomycosis-associated mortality in a multivariable analysis. All racial/ethnic minorities also had higher mortality rates as compared with non-Hispanic Whites: Hispanic (OR: 2.10, 95% CI: 1.53, 2.88), African American (OR: 3.42, 95% CI: 2.55, 4.60), Asian (OR: 5.51, 95% CI: 2.82, 10.70), and Native American (OR: 2.18, 95% CI: 1.52, 3.12).[73] This analysis did not control for comorbidities. These studies assumed that causes of death were accurately recorded on death certificates. A subsequent capture-recapture study compared ascertainment of deaths by death certificates and hospital discharge data (i.e., in-hospital mortality). Coccidioidomycosis-associated deaths were underestimated seven-fold by death certificates as compared with the estimate derived from hospital discharge data and death certificates.[92]

Coccidioidomycosis and Community-acquired Pneumonia

Several studies have suggested that coccidioidomycosis is a common cause of community-acquired pneumonia (CAP) in Arizona, yet testing is relatively infrequent. In a prospective study, Valdivia et al. estimated the proportion of CAP due to coccidioidomycosis among adult outpatients seen at three facilities in Tucson in 2003–2004. CAP was defined as lower respiratory symptoms of less than one-month duration with either chest pain, exertional dyspnea, chest x-ray, multiple visits for their illness, or a CAP-associated antibiotic prescription. Patients with a history of coccidioidomycosis, less than one week spent in an endemic area, or another laboratory-confirmed diagnosis were excluded. Serological testing was conducted at two visits, a median of 18 days apart. Of 55 included patients, 29% (95% CI: 16, 44) had a positive test. Only 19 patients provided both serum specimens. The true proportion of patients with positive results may be higher if some of the remaining patients subsequently seroconverted.[86] A smaller study in Phoenix had similar findings: of 35 adult patients with pneumonia (including

pulmonary infiltrate) and prospectively collected paired sera available for testing, 17% (95% CI: 7%, 34%) had antibody seroconversion.[93]

Chang et al. estimated the proportion of CAP patients tested for coccidioidomycosis in a retrospective cohort assembled from two health systems in the Phoenix metropolitan area. Medical records for outpatients an ICD-9 discharge code pneumonia due to infection admitted in 2003 and 2004 were reviewed. Patients without a history of coccidioidomycosis and physician-diagnosed CAP who had not been hospitalized or been residents of a long-term care facility within 14 days of symptom onset were included in the study. In system A, only one of 66 patients was tested, while in system B, 11 (13%) of 87 patients were tested.[85] A 2004–2006 study of 125,000 patients with a diagnosis code for CAP among three million Medicaid enrollees found that only 4% of patients had *Coccidioides* serology or fungal culture ordered within 90 days of diagnosis.[94]

In response to these findings, efforts have been undertaken to increase the number of CAP patients tested for coccidioidomycosis. An educational intervention consisting of lectures and posters reminding physicians to test for coccidioidomycosis was implemented in two large emergency departments in Tucson between 2007 and 2008. The proportion of CAP patients tested for coccidioidomycosis increased from a pre-intervention level of 10% to 40% over one year.[95] However, only 3% of CAP patients presenting at emergency departments in Arizona in 2014 were tested for coccidioidomycosis, and there was substantial variation in testing across facilities and providers, even in the highly endemic counties.[96]

Surveillance in Arizona

The first case of coccidioidomycosis in Arizona was described in 1938.[45] Clinicians began reporting cases of coccidioidomycosis in Arizona to the state health department in the

1950's.[97] In 1994, the state health department adopted the national case definition proposed by the Council of State and Territorial Epidemiologists. Before 1994, surveillance was based on clinical diagnosis and laboratory confirmation was not required.[49] In 1995, coccidioidomycosis became nationally notifiable in the southwest region.[65] In 1997, the state health department mandated laboratory reporting of all positive *Coccidioides* laboratory results and adopted a case definition requiring only laboratory confirmation to define a confirmed case.[75,98] Laboratory criteria were also modified from requiring a rise in *Coccidioides* IgG titer to a single positive *Coccidioides* IgG result. The national case definition adopted the latter criterion in 2008.[98] However, this laboratory-based definition of confirmed cases is unique to Arizona. An interview study of 493 cases reported in 2007–2008 found that 95% met the clinical criteria of the national case definition.[75]

Only name, age, gender, residential address, laboratory result(s), and reporting provider and/or testing laboratory are typically included in case reports to ADHS. In 2015, 99% of cases were reported by laboratories.[45] A surveillance evaluation of *Coccidioides* laboratory result reporting by the two largest reference laboratories in the state was conducted in 2008. Reports from the two laboratories were matched to state surveillance databases. The proportions of patients tested by each laboratory matching a surveillance record were 98% and 85%.[95] Since then, both laboratories have adopted electronic laboratory reporting and completeness of case and laboratory result reporting has likely improved. Surveillance changes, which are discussed in detail below, complicate the interpretation of trends. Case reports appear to have increased independently of surveillance changes as well.

Box 1-1. Arizona Department of Health Services Coccidioidomycosis Case Definition[99]

Clinical Description

Infection may be asymptomatic or may produce an acute or chronic disease. Although the disease initially resembles an influenza-like illness 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, including fever, chest pain, cough, myalgia, arthralgia, headache
- Pneumonia or other pulmonary lesion, diagnosed by chest X-ray
- Rashes, including erythema nodosum or erythema multiforme
- Involvement of bones, joints, or skin by dissemination
- Meningitis
- Involvement of viscera and lymph nodes

Laboratory Criteria for Diagnosis

Laboratory-confirmed coccidioidomycosis requires at least one of the following:

- Cultural, histopathologic, or molecular evidence of presence of *Coccidioides* species, OR
- Immunologic evidence of infection
    - Serologic (testing of serum, cerebrospinal fluid (CSF), or other body fluid) by:
        - Detection of coccidioidal IgM by immunodiffusion, enzyme immunoassay (EIA), latex agglutination, or tube precipitin, OR
        - Detection of coccidioidal IgG by immunodiffusion, enzyme immunoassay (EIA), or complement fixation (for complement fixation, titers from blood

must be ≥ 1:4; for immunodiffusion or when the specimen is CSF, any titer is considered positive).

- Coccidioidal skin test conversion from negative to positive after the onset of clinical signs and symptoms.

Case Classification

Confirmed - A case that is laboratory confirmed.

CHAPTER 2: LITERATURE REVIEW

Surveillance Changes

Surveillance changes are a major challenge to understanding trends in coccidioidomycosis incidence. Clinicians began reporting cases of coccidioidomycosis in Arizona to the state health department in 1954.[100] In 1994, the state health department adopted the national case definition proposed by the Council of State and Territorial Epidemiologists. Before 1994, surveillance was based on clinical diagnosis, and laboratory confirmation was not required.[49] In 1997, the state health department mandated laboratory reporting of all positive *Coccidioides* laboratory results and adopted a case definition requiring only laboratory confirmation to define a confirmed case.[75,98] Laboratory criteria were also modified from requiring a rise in *Coccidioides* IgG titer to a single positive *Coccidioides* IgG result. The national case definition adopted the latter criterion in 2008.[98] Until 2019, this laboratory-based definition of confirmed cases was unique to Arizona.[101] An interview study of 493 cases reported in 2007–2008 found that 95% met the clinical criteria of the national case definition.[75]

In June 2009, a large commercial reference laboratory ('Lab A') in Arizona began reporting all positive *Coccidioides* enzyme immunoassay (EIA) results without positive confirmatory tests to the state health department. During this time, Lab A reported 40–60% of cases reported to the state health department. Prior to this point, Lab A reported only results for EIA IgM and/or IgG positive patients who were also positive by immunodiffusion. State reporting rules required reporting of all positive EIA results; the 2008 revision of the national case definition specified that an isolated EIA positive result fulfills laboratory criteria for defining a confirmed case. Simultaneously, Lab A began reporting all positive EIA results to providers with a statement stating that specimens positive only on EIA might be false positives. On November 26th, 2012, Lab A switched from the Premier *Coccidioides* EIA produced by

Meridian Biosciences to the Omega *Coccidioides* antibody EIA produced by Immuno-Mycologics (IMMY). Case counts increased 214% from 2008 to 2009 and decreased 55% from 2012 to 2013. The 2009 change was also associated with a shift in age and sex distributions towards younger, female patients.[97] The impact of these changes on healthcare provider behavior (i.e., the likelihood of a patient being tested) is unknown.

The Premier *Coccidioides* EIA produced by Meridian Biosciences has been in use for over 15 years. Microwells are coated with purified TP and CF antigens in the same well.[41] The reported sensitivity (Se) and specificity (Sp) of the assay were 92% and 97% for IgG, and 74% and 96% for IgM, and 97% and 94% in combination (i.e., if IgM and/or IgG positive), respectively.[43,102,103] The assay cross-reacts with serum from patients with histoplasmosis, but this disease is rare and not reportable in Arizona.[104] This assay requires a wash step.[105] At Lab A, the Meridian assay was performed with an automated wash step. The Omega *Coccidioides* antibody EIA produced by IMMY has separate microwells for IgM and IgG ascertainment and uses recombinant and natural antigens.[41] This assay has a reported combined IgM and IgG Se and Sp of 94.1% and 98.7% compared to complement fixation.[41]

While the *Coccidioides* EIA is likely more sensitive than other tests, reports in the literature have questioned the specificity of results.[106,107] Assessment of EIA performance is complicated by several factors: the assay used; the method by which the assay is performed; study inclusion and exclusion criteria, especially the reason for testing and its implications for the prevalence of disease in the study sample; the use of control sera collected from people residing in areas where the infection is endemic; the lack of a clear diagnostic gold standard; and the small sample size of some studies.

Several studies have evaluated the real-world performance of the *Coccidioides* EIA and described the clinical characteristics of patients with positive EIA results and no other positive tests. Blair et al. reviewed medical records for 405 patients with positive Meridian *Coccidioides* EIA results seen at their institution to assess the significance of EIA IgM positive, IgG negative results. Twenty-eight patients had a positive EIA IgM test and a negative EIA IgG test. Of these, 24 had a concurrent positive immunodiffusion or complement fixation test or a subsequent positive EIA IgG and the remaining four had a positive culture or biopsy. Thus, they concluded that all of these patients had coccidioidomycosis and that none had false positive EIA results.[108] A subsequent expanded study by these authors of 102 patients with at least one EIA IgM positive/IgG negative set of results found that 22% (n=22) did not have a coccidioidomycosis diagnosis. Fifty-nine percent (n=60) of these patients were tested to evaluate coccidioidomycosis-compatible symptoms (i.e., diagnostic evaluation) and 90% of patients in this subgroup had confirmed or probable coccidioidomycosis. Twenty eight percent (n=29) of the overall sample were tested for screening purposes and of this subset, only 45% had confirmed or probable illness. However, 17% (n=5 of 29) of these patients later became IgG positive. Patients in these studies were tested using the Meridian EIA kit run with an automated wash step.[109]

Oubsuntia et al. tested 1,682 serum specimens submitted to their reference laboratory as part of routine clinical testing in a highly endemic area (Kern County, California) using the Meridian EIA, immunodiffusion, and immunodiffusion with concentrated serum. Only EIA IgM results were provided. Of the 15% of specimens with positive or indeterminate EIA IgM results, 44% were positive by one or both immunodiffusion modalities. EIA IgM absorbance values for

specimens that were concentrated immunodiffusion negative overlapped with positive samples. Further results for this study could not be located.[110]

Kuberski et al. reviewed records for 17 patients with positive EIA IgM and negative EIA IgG test results. Upon chart review, only three "may have had coccidioidomycosis." However, no inclusion or exclusion criteria were defined, and it is unclear if patients had additional serologic testing.[106] Crum et al. reviewed records for all patients with positive Meridian *Coccidioides* EIA results seen at their facility in San Diego, California between 1994 and 2002. Of 223 patients, 48 (22%) had isolated positive EIA IgM results. None of these patients were diagnosed with coccidioidomycosis; diagnoses included upper respiratory infection, asymptomatic "surveillance testing", and community-acquired pneumonia. Patients with isolated IgM results were more likely to be immunosuppressed.[107] Petein et al. reviewed all serologic test results from Lab A and another commercial laboratory between February 2008 and February 2009. They identified 94 of 1,445 sets of tests in which EIA IgM and/or IgG was positive and complement fixation and/or immunodiffusion was negative. Forty (42%) had a positive EIA IgM test only. Upon review of medical records, 97% of these 94 patients had symptoms consistent with coccidioidomycosis.[111]

Lindsley et al. evaluated the specificity of the two EIA kits using 534 serum specimens collected from people living in Puerto Rico who had not traveled outside of Puerto Rico in the 14 days prior to serum collection and 1,218 serum specimens from a northwest Phoenix blood bank. Serum from EIA positive specimens were concentrated and tested with immunodiffusion. This study found no significant difference in EIA reactivity between the Meridian and IMMY assays for sera from Puerto Rico (i.e., non-endemic controls). However, fewer Phoenix serum specimens were IgM reactive for the IMMY assay than the Meridian assay (1.1% vs. 2.4%). IgG

reactivity was similar (3.2 vs. 3.6%). For both assays, the proportion of specimens that were IgG positive was greater among the Phoenix sample compared with the Puerto Rico sample. IgM reactivity in the Puerto Rico sample likely represents false-positive results, possibly due to cross-reactivity. However, IgM and IgG reactivity in the Phoenix sample may represent past infection or current asymptomatic infection. Concentration yielded additional positive results in the Phoenix sample only; a greater proportion of Meridian-positive (IgM or IgG) sera were subsequently positive on post-concentration immunodiffusion. Immunodiffusion reactivity only after concentration suggests very low levels of antibodies.[41]

A recent study conducted at a tertiary care center in the Phoenix metropolitan area examined the sensitivity and specificity of both EIA kits using a composite gold standard.[112] The gold standard reflected varying levels of diagnostic certainty ranging from confirmed (culture or histopathology indicative of coccidioidal infection) and highly probable (compatible symptoms, radiographic findings, and positive complement fixation and/or immunodiffusion) to probable (compatible symptoms or radiographic findings and positive complement fixation and/or immunodiffusion). Coccidioidomycosis negative patients lacked compatible symptoms and radiographic findings, but could have positive complement fixation and/or immunodiffusion results. There were 49 composite positive patients and 152 negative patients with remnant sera available for testing. Indications (e.g., diagnostic vs. screening) for initial testing were unknown. Indeterminate EIA results were considered to be positive. Of note, the authors compared automated vs. manual runs of the Meridian EIA and found no meaningful differences in results. Results from automated runs are discussed here. Combined IgM and IgG sensitivity was slightly lower for the IMMY kit: 83.7% (95% CI: 70.3, 92.7 for the Meridian kit) vs. 73.5% (95% CI: 58.9, 85.1 for the IMMY kit). Combined specificity was higher for the IMMY kit: 68.4% (95%

CI: 60.4, 75.7 for the Meridian kit) vs. 82.2% (95% CI: 75.2, 88.0 for the IMMY kit). However, performance varied by antibody. Sensitivity for IgM antibody was substantially lower for the IMMY kit (34.7%, 95% CI: 21.7, 49.6) compared with the Meridian kit (57.1%, 95% CI: 42.2, 71.2) while specificity was higher (85.5%, 95% CI: 78.9, 90.7 for the IMMY kit vs. 70.4%, 95% CI: 62.5, 77.5 for the Meridian kit). Results were more similar for the IgG antibody. Sensitivity was higher for the Meridian kit (69.4%, 95% CI: 54.6, 81.7) as compared with the IMMY kit (53.1% 95% CI: 38.3, 67.5). However, specificity did not differ substantially (95.4% vs. 96.7% for the Meridian and IMMY kits, respectively).

A study by Khan et al. compared the performance of these two kits at Lab A and two other reference laboratories. Sera from 150 clinically confirmed coccidioidomycosis cases and 50 controls (CDC employees from non-endemic areas) were tested by both assays at all three laboratories. Percent agreement was highest for IMMY EIA IgM (90%) and lowest for Meridian EIA IgM (67%). Specificity of combined EIA IgM and IgG result for IMMY ranged from 98–100%. Specificity of the Meridian EIA was 100% at the other two reference laboratories, but only 74% at Lab A.[113] This comparison of results by the Meridian assay at Lab A using the automated wash step procedure and the IMMY assay will be used in Aim 1.

Weather

The study of weather and coccidioidomycosis is motivated by several goals: 1) to understand the ecological relationship between climate and *Coccidioides* growth; 2) to quantify the relationship between weather and risk of coccidioidomycosis; and 3) to predict disease incidence and mitigate risk (i.e., an early warning system to warn the general public). Although (3) would have the greatest public health impact, studies have primarily focused on (2). Climate

change has also heightened interest in prediction of future coccidioidomycosis risk and possible expansion of endemic areas.

Environmental factors, particularly climate, have long been thought to be associated with the growth of *Coccidioides* and dispersal of arthroconidia. Factors hypothesized to affect growth and dispersal include precipitation, temperature, relative humidity, dust storms, soil characteristics (moisture, salinity and concentration of other trace elements, organic matter, pH), competing soil microbes, rodent activity, Paleo-Indian archaeologic sites, vegetation, and the presence of desert washes and stream beds or banks.[8]

Water plays a central role in the lifecycle of *Coccidioides*. Moisture is required for the fungus to grow. Soil samples taken during the end of the wet season in the San Joaquin Valley in California were more likely to test positive for *Coccidioides* than those sampled at the end of the dry season.[114] Samples were most likely to test positive six weeks after rainfall.[115] Similarly, in Arizona, positive samples were more likely to have been collected following the summer rains.[6] However, very wet conditions may allow other organisms in the soil to outcompete it, which may explain why *Coccidioides* is found in arid environments.[8,116] Moisture may also decrease the ability of arthroconidia to become airborne.[3] Thus, precipitation may affect both *Coccidioides* growth and dispersal: too little rainfall and growth may not occur, too much and competitors may inhibit growth. The relationship between precipitation and soil moisture is determined not only by total rainfall, but also temperature, vapor pressure, evaporation, runoff, and soil characteristics.[8] Precipitation may affect the concentration of salts at varying soil depths; increased salinity (e.g., of borate salts) was associated with enhanced growth and survival of cultures in laboratory studies. An extensive soil sampling study of the same area in the San Joaquin Valley conducted over eight years found that soluble salt concentration was correlated

with *C. immitis* detection.[114] Lacy and Swatek observed that growth of the mycelium in soil required 56–90% relative humidity for several weeks.[7]

Precipitation in southern and central Arizona is bimodal, occurring in the winter and spring and in the late summer (July – September) as the North American monsoon. Summers are hot and dry.[8] Precipitation during the late summer may vary substantially across space and time due to thunderstorms. Winter precipitation events last longer than summer storms, which are characterized by bursts of rain. The El Niño-Southern Oscillation is one of the drivers of interannual variability in precipitation in the Southwest.[117] In Arizona, an El Niño is associated with a higher likelihood of above average precipitation between October and March.[118]

Precipitation has been the most widely studied potential determinant of coccidioidomycosis incidence. Hugenholtz found zero to weak positive correlation between semimonthly rainfall (range: 0.02–0.16) and case count.[55] Kolivras and Comrie examined the relationship between minimum, maximum and mean monthly precipitation and deviation from mean monthly percent of annual total cases reported in 1948–1972 and 1980–1998 in Pima County. Standardized coefficients ranged from -0.524 (1-year lagged November-December precipitation and March incidence anomaly) to 0.568 (2-year lagged February-March precipitation and March incidence anomaly).[117] Comrie found that one-year lagged May-July precipitation was associated (standardized coefficient range: 0.45, 0.73) with increased incidence in subsequent seasons (monsoon, fall, and winter) between 1992 and 2003 in Pima County. Other relationships varied by season and are difficult to interpret.[119]

Park et al. 2005 found that cumulative rainfall during the previous seven months (RR 0.86 95% CI: 0.81, 0.91), and cumulative rainfall during previous two months divided by cumulative rainfall during previous seven months (RR 0.55 95% CI: 0.68, 0.93) were inversely

associated with monthly incidence rate in Maricopa County between 1998 and 2001.[65] Tamerius and Comrie found consistent relationships between precipitation and incidence by county: October-December precipitation was associated with a 0.01 (95% -0.01, 0.03) increase in mean reporting delay-adjusted August-March incidence rate while August-March precipitation was associated with a -0.01 to -0.005 (95% CI -0.01, 0.03 and -0.02, 0.01) decrease in incidence rate.[120] Tong et al. reported negative correlations (range: -0.10, -0.45) between annual and seasonal (spring, early spring, prior winter) precipitation anomaly (deviation from 1990–2010 mean) and incidence rates in Maricopa and Pima counties.[121] Gorris et al. found that four-month lagged mean monthly precipitation was correlated with incidence rates in Arizona (R=0.68) in the bivariate analysis, but only two-month lagged precipitation (-0.17) was significant in the multivariable model.[122,123] Kolivras and Comrie and Park et al. also examined the relationship between drought severity, as measured by the Palmer Z Index and the Palmer Drought Severity Index (PDSI), and incidence. No associations were found.[65,117]

Studies have also examined direct and indirect measures of soil moisture, possibly a more relevant determinant of fungal growth than rainfall alone. Stacy et al. examined the relationship between normalized difference vegetation index (NDVI), a remotely sensed measure of vegetation density and indirect measure of soil moisture, and incidence in Maricopa, Pima, and Pinal counties between 1995 and 2006. The relationship between concurrent and lagged seasonal NDVI and grouped incidence was highly variable and inconsistent across counties.[124] Two studies have used remotely sensed soil moisture measures. Coopersmith et al. found that mean soil moisture at 5 cm during May–July was inversely correlated (correlation coefficient range: -0.55, -0.45) with January–May monthly incidence in Maricopa, Pima, and Pima between 2000

and 2014.[125] Gorris et al. did find that one-month lagged soil moisture (-0.19) and NDVI (-0.28) were negatively correlated with monthly incidence anomaly between 1990 and 2014.[122,123]

Temperature may be an independent driver of the lifecycle. High temperatures may "sterilize" the surface of the soil and inhibit competing organisms.[8] *Coccidioides* may be better adapted to surviving these temperatures.[6,115,126] In the laboratory, *C. immitis* arthroconidia were viable for six months at a broad range of temperatures and relative humidity levels.[127] The relationship between temperature and incidence has also been examined by several studies. Hugenholtz found that mean monthly temperature and number of cases per month at Williams Air Force Base between 1943 and 1956 were highly correlated (R^2 0.73).[55] Kolivras and Comrie found distinct relationships between minimum, maximum, and mean monthly temperature and incidence anomaly. Temperature (lagged 0.5–3.5 years) was associated with incidence anomaly for all months. Standardized coefficients ranged from -0.608 (one-year lagged July–September temperature and July incidence anomaly) to 0.632 (concurrent May–September temperature and October incidence anomaly).[117] The variation in lags and groupings by month complicates interpretation of their findings. Park et al. found that average temperature during the previous three months was associated (RR 1.012 95% CI 1.007, 1.020) with monthly incidence in Maricopa County.[65] Gorris et al. found that four-month lagged temperature was correlated (R=0.54) with incidence rates in the bivariate analysis, but not the multivariable model.[122,123] Tamerius and Comrie found no significant correlation between surface temperature and reported incidence.[120]

Coccidioides arthroconidia are spread by aerosolization and have a relatively low settling rate.[3] Outbreaks of coccidioidomycosis have occurred in association with wind and other natural soil disturbances. In 1977, a large dust storm in Central California deposited soil from highly

endemic areas to parts of northern California; an increase in infections was observed several weeks later.[128] In 1994, a landslide caused by the Northridge earthquake produced large dust clouds and resulted in 203 excess cases in Ventura County, California.[129] Dust control measures undertaken in the 1940s at Army bases in central California were associated with a decrease in incidence.[130] Notably, the annual number of dust storms in the Southwest has increased over time, possibly driven by changes in sea surface temperatures in Pacific Ocean and the Pacific Decadal Oscillation.[131]

Several studies have sought to use measures of dust concentration to approximate density of airborne arthroconidia. Hugenholtz found positive correlations (range: 0.47–0.67) between the number days with dust storms of over one-hour duration and monthly case count at Williams Air Force Base between 1943 and 1956.[55] Park et al. found that the concentration of airborne particles of 10 microns or less in diameter (PM10) was associated (RR 1.015, 95% CI 1.007, 1.024) with monthly coccidioidomycosis incidence in Maricopa County between 1998 and 2001.[65] Comrie found that concurrent PM10 was positively associated with reporting delay adjusted mean May–July (standardized coefficient 0.75) and January–April (standardized coefficient 0.44) incidence rate in Pima County.[119] Tong et al. examined the correlation between annual number of dust storms in the southwestern U.S. and 2001–2011 reported incidence. Dust storms were identified using a previously developed method based on ground aerosol observations and differentiation of manmade and natural dust sources by elemental composition.[131] Dust storms were correlated with incidence in Maricopa and Pima counties (R=0.51 and 0.41, respectively). However, PM10 and PM2.5 were all negatively correlated with incidence.[121] Gorris et al. found weak correlation (R=0.23) between remotely sensed one-month lagged mean monthly surface dust concentration and monthly incidence in Arizona.[122,123] Three

studies have examined the relationship between wind speed and vector and incidence: Tamerius and Comrie (monthly and seasonal mean wind speed and vector),[120] Park et al.(monthly and previous two month mean wind speed),[65] and Kolivras and Comrie (monthly mean wind speed).[117] No associations were found between incidence and wind speed and vector.

An environmental link is also supported by the seasonality of human infections. Seasonality of reports has long been observed in cases reported to ADHS (Figure 2-1). Reports generally peak in December with a second peak sometimes observed in the late summer. Reports reach a nadir in the late spring. Exceptions to this pattern include cases reported in 2011, when little seasonality was observed, and 2015, whereas cases peaked in September. Coccidioidomycosis cases at the University of Arizona student health clinic in Tucson similarly had two annual peaks.[54] Coccidioidomycosis hospitalizations at Williams Air Force Base in Maricopa County from 1952 to 1956 peaked in July and in the fall (October/November).[55]

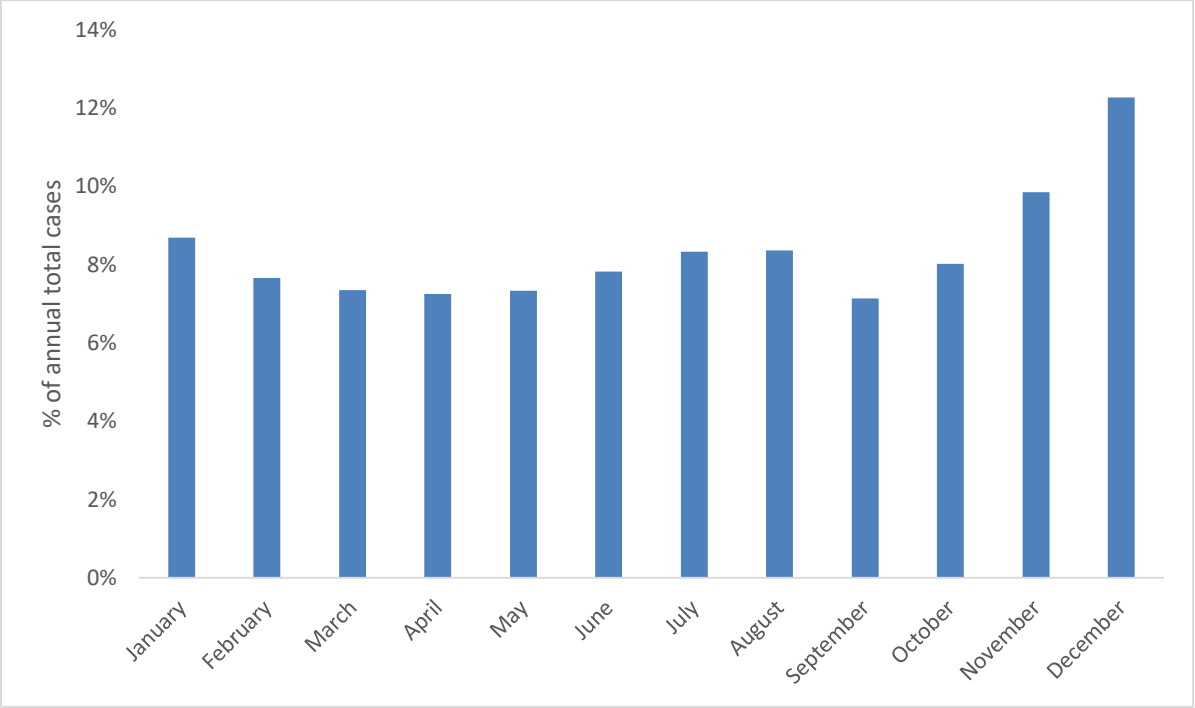


Figure 2-1. Seasonality of reported coccidioidomycosis in Arizona, 1998–2016

This seasonality motivates the study of the relationship between climate and incidence. As discussed above, numerous studies have quantitatively examined the relationship between weather and the incidence of reported coccidioidomycosis in California and Arizona. Relationships have not been studied in Mexico, Central and South America. Table 2-1 summarizes results from studies of weather and coccidioidomycosis in Arizona. Results are difficult to compare because of differences in the study periods, data sources, and transformations applied to predictor (e.g., seasonal means) and outcome (e.g., reporting delay adjustment) variables. Only Brown et al. adjusted for explicitly adjusted for surveillance changes.[132] Comrie and Glueck explored the impact of adjusting for reporting delay (using a 3-month running mean of onset-to-report time vs. a 1 month-offset) and found that lack of adjustment did not affect the main results of their analysis, though variance explained decreased for two of four seasonal models.[133] Box 2 summarizes key methodological issues for these studies.

In summary, studies have found associations of varying magnitudes between precipitation, temperature, PM10, dust storm frequency, season, and soil moisture and incidence. Other factors examined for which no significant relationship has been observed were dew point temperature[117], relative humidity, vapor pressure deficit, and solar radiation heat units.[120] The timing and magnitude of effects are inconsistent across studies. Several studies point to a relationship between lagged precipitation (or soil moisture), temperature, and incidence, although lags vary between four months and three years and by geographic region.

Box 2-1. Methodological Issues for Weather and Coccidioidomycosis Studies

- Incidence is an indirect measure of *Coccidioides* growth and spore dispersal
    - Growth in the natural environment is not measured
    - Arthroconidia concentration has not been measured
    - Not all strains may be virulent or equally affected by climate factors
- Lack of biological evidence to support lagged relationships
- Surveillance changes
- Delay between exposure and case report (variability in delay, lack of symptom onset dates)
- Unexplained long-term linear increase in incidence
- Population denominators include immune individuals
- Sample size of annually/seasonally grouped analyses
- Choice of transformations of incidence and weather variables
- No out-of-sample tests of models

Table 2-1. Summary of climate and coccidioidomycosis studies in Arizona

Study	Study Period	Study Area	Predictors	Outcome	Methods	Major Findings
Brown et al. (2014)	1995–2013	Maricopa	Seasonal total precipitation	Linear detrended monthly and seasonal "exposure" rate calculated by subtracting incubation period and median onset to diagnosis time from enhanced surveillance study. Two seasonal groupings.	Adjusted for 2009–2012 change in surveillance by standardization. Regression coefficients from Tamerius and Comrie (2011) applied.	Tamerius and Comrie (2011) model predictions did not match observed case counts in 1998, 2008–2010.
Comrie (2005)	1992–2003	Pima	Seasonal PM10 and total precipitation	Mean onset-to-diagnosis and onset-to-report lag times were calculated for each individual month in the record. Grouped into four seasons defined by maxima and minima of each variable.	Linear regression with predictors concurrent PM10 and concurrent and lagged precipitation. Seasons modeled separately.	Concurrent PM10 associated with rates in winter and foresummer (May–July). Previous foresummer's precipitation associated with increased incidence in 3/4 seasons. R^2 highest for foresummer and winter.

Comrie and Glueck (2007)	1992–2005	Pima	Seasonal PM10 and total precipitation	Same as Comrie (2005)	Same as Comrie (2005)	Nearly identical to Comrie (2005)
Coopersmith et al. (2017)	2000–2014	Maricopa, Pima, Pinal (combined)	Mean monthly satellite-derived soil moisture at 5cm. Grouped into 3-month periods.	Linear detrended rate of reported cases per month.	Correlation analysis of lagged soil moisture and incidence.	Preceding May–July (foresummer) mean soil moisture inversely associated with Jan–May monthly incidence.
Gorris et al. (2017)	1990–2015	Maricopa, Pima, Pinal (combined)	Surface temperature, precipitation soil moisture up to 10 cm, NDVI surface dust concentration.	Monthly incidence anomaly (reported case count – study period mean for each month)	Correlation between lagged and concurrent predictors and incidence. Linear and non-linear regression	Incidence anomalies negatively correlated with precipitation (-0.17) and soil moisture (-0.19) anomalies in the previous 1–2 months, positively correlated with surface dust (0.23) in the previous month, and negatively correlated with same month NDVI (-0.28).

Hugenholtz et al. (1957)	1952–1956	Maricopa County (Williams Air Force Base)	Precipitation, temperature, and dust storms.	Monthly hospital admissions	Correlation analysis.	High incidence months were associated with lower rainfall. Incidence was most strongly correlated with temperature and dust storms.
Kolivras and Comrie (2003)	1948–1972, 1980–1998	Pima	Monthly mean, min, max temperature, dew point temperature, precipitation, Palmer Drought Severity Index (PDSI), mean wind speed.	Monthly percent of annual total reported cases. Deviation from mean monthly percent of annual total calculated for each month.	Bivariate correlation analysis of 1–24-month lagged predictors and outcome. Linear regression models for each month.	Differing results by month, but most models included 1–2-year lagged variable. Winter temperature and precipitation included in several models. R^2 range 0.21–0.61.
Park et al. (2005)	1998–2001	Maricopa	Palmer Z index, PDSI, PM10, mean wind velocity (concurrent and previous 2 months), average temperature (previous three	Monthly reported case count.	Poisson regression. Modeling strategy unclear.	Final model included mean temperature during previous 3 months (positive), mean PM10 (positive), cumulative rainfall during previous 7 months

			months), average dust, rainfall (previous 3 months), cumulative rainfall (previous 7 months), total rainfall previous 2 months/total rainfall previous 7 months.			(negative), cumulative rainfall during previous 2 months/cumulative rainfall during previous 7 months (negative).
Stacy et al. (2013)	1995–2006	Maricopa, Pima, Pinal	Seasonal normalized difference vegetation index (NDVI)	Linear detrended seasonal incidence rate. Subtracted 14-day incubation period and diagnosis delay offset calculated by polynomial fit to time series of average monthly offsets. Four seasonal groupings.	Bivariate correlation for concurrent and 1- to 48-month lagged NDVI and exposure rate. Stepwise multivariable linear regression with leave-one-out cross-validation. Each season modeled separately.	Winter precipitation results in moist soils in the early spring and is correlated with grouped seasonal incidence up to a year later. Strength and direction of relationships varied widely across seasons.

Tamerius and Comrie (2011)	1995–2006	Maricopa, Pima	Monthly and seasonal temperature, relative humidity, wind speed, mean wind speed vector, vapor pressure deficit, precipitation, solar radiation, heat units, PM10.	Linear detrended monthly and seasonal "exposure" rate calculated by subtracting incubation period and median onset to diagnosis time from enhanced surveillance study. Two seasonal groupings.	Autocorrelation analysis to create seasonal groupings. Bivariate correlation analysis of predictors. Linear regression model: preceding Oct–Mar precipitation and concurrent Sep–Mar precipitation to estimate Aug–Mar exposure rate.	Variance of exposure rates increased over time. Antecedent precipitation positively and concurrent precipitation negatively correlated with seasonal exposure rate.
Tong et al. (2017)	2001–2011	Maricopa, Pima (combined)	Annual number of dust storms, PM10, PM2.5, precipitation anomaly.	Annual rate of reported cases.	Bivariate correlation analysis.	Dust storms were positively correlated with incidence (R=0.41–0.51)

Land Development

Anthropogenic soil disturbance has long been associated with coccidioidomycosis, particularly point-source outbreaks. An early description of coccidioidomycosis was an outbreak among a group of students who dug a rattlesnake out of a ground squirrel burrow in Kern County, California.[24,28] Half (n=25) of all outbreaks reported in the literature were linked to occupational land disturbance (e.g. construction, archaeology, military field exercises).[52] Central and southern Arizona have undergone rapid urbanization and population growth during the last 30 years. The population of the Phoenix metropolitan area (most of Maricopa County and part of Pinal County) increased 87% between 1990 and 2010.[134] While urban expansion in the early twentieth century used primarily core agricultural lands, growth since 1975 has consumed native desert land. Peripheral expansion has profoundly altered natural systems and brought populations closer to areas where desert soils are being disturbed.[135]

Several studies have examined the relationship between land development and coccidioidomycosis in Arizona. Blair et al. compared the one-year risk of coccidioidomycosis in employees at a healthcare facility adjacent to a construction site with workers at another campus located elsewhere in the Phoenix metropolitan area. As the coccidioidal skin test was unavailable, an in vitro lymphocyte-activation assay was used to measure cellular immunity to coccidioidomycosis, allowing the detection of asymptomatic infections. Contrary to their hypothesis of increased risk of infection at the site adjacent to construction and excavation of native desert soil, the investigators found a higher risk of infection at the control site. They hypothesized that the focal distribution of fungi (no soil sampling was conducted), false negative tests, and/or dust suppression measures may explain their unexpected results.[47]

Park et al. mapped 1998–2001 age-adjusted incidence rate in Maricopa County and noted high rates in areas undergoing construction and development along the periphery of metropolitan

Phoenix. There was no association between monthly coccidioidomycosis case reports and number of building permits issued in Maricopa County between 1998 and 2001, though issue dates of building permits likely do not coincide with construction and soil excavation.[65] Moreover, building permits are issued for a variety of activities, not all of which involve soil excavation. The analysis did not account for the location for which the permit was issued (e.g., native desert area vs developed land) and the location of incident case reports.

Pianalto et al. examined the relationship between construction-related soil disturbance, which was estimated from a model of fugitive dust emissions from remote sensing data, and lagged incidence between 1995 and 2006 in Pima County. At the county-level, annual construction-related disturbance and lagged incidence were highly correlated (Spearman's rank order correlation: 0.81). This study also examined the correlation between ZIP code-level incidence and soil disturbance. Analyzed by ZIP code, there was modest correlation (adjusted R^2=0.48) between total incidence during the entire study period and disturbance in ZIP codes at the periphery of Tucson and no correlation at inner or core Tucson ZIP codes.[136]

Coccidioidomycosis reports have increased over time in Antelope Valley, an area north of Los Angeles abutting the hyperendemic area in California. Rapid, suburban expansion has been hypothesized to contribute to increasing incidence. Colson et al. examined the correlation between 2000–2015 coccidioidomycosis incidence and land disturbance in this area. The area experienced rapid development of housing and renewable energy projects. Coccidioidomycosis incidence increased 13-fold between 2000 and 2015. Acres of land disturbed for solar, wind, and agricultural use was correlated with incidence (R^2 = 0.62); in the multivariable model, land disturbance was the only significant predictor, although the magnitude of the effect was extremely small (β = 0.00040).[137] Guevara et al. found that the number of reported new

residential buildings in Antelope Valley was correlated ($R^2 = 0.85$) with coccidioidomycosis incidence rate in Los Angeles County between 1996 and 2007; construction outside of Antelope Valley was not strongly correlated with incidence. While construction has decreased since 2005, incidence rates have not consistently declined since then. In Los Angeles County as a whole, cases residing in endemic health districts were more likely to report exposures associated with outdoor exposure (being in sight of construction and earth excavation, dust storm, outdoor recreational vehicles, any outdoor recreation, outdoor activity with dirt) than cases in non-endemic districts.[138]

The choice of spatial scale and unit of aggregation can have a significant impact on spatial risk assessment. Brown et al. examined the association between several areal characteristics and incidence for 2006–2009 cases in Arizona at the case residence, block group, tract, and ZIP code scales. Factors associated with incidence across scales included population over 65 (positive), median income (positive), soil organic carbon (negative), medium and high density residential land (positive), pasture/hay land (negative), and distance to desert (negative). Associations with shrub/scrub land, cultivated crops, and distance to wetland varied in magnitude and/or direction by spatial scale.[68]

CHAPTER 3: BIAS-ADJUSTED TRENDS IN REPORTED COCCIDIOIDOMYCOSIS INCIDENCE IN ARIZONA, 1998–2017

Background

Coccidioidomycosis is an infectious disease caused by inhalation of spores produced by *Coccidioides* species, fungi endemic to desert soils of the Americas.[1] Nearly two-thirds of all cases reported in the United States between 1998 and 2017 occurred among people living in Arizona. Since the State mandated laboratory reporting of positive *Coccidioides* laboratory test results in 1997, rates of reported disease have increased five-fold.[97] It is one of the most frequently reported infectious diseases in Arizona. Rates of reported coccidioidomycosis between 1998 and 2017 ranged from 30 cases per 100,000 person-years (1,556 cases) in 1998 to 255 cases per 100,000 person-years (16,472 cases) in 2011.[139] The causes of this increase are poorly understood.

Surveillance changes are a major challenge to understanding trends in coccidioidomycosis incidence. Clinicians began reporting cases of coccidioidomycosis to the Arizona Department of Health Services (ADHS) in the 1930s.[97] In 1994, the state health department adopted the national case definition proposed by the Council of State and Territorial Epidemiologists; before 1994, surveillance was based on clinical diagnosis, and laboratory confirmation was not required.[49] In 1997, the state health department mandated laboratory reporting of all positive *Coccidioides* laboratory results and adopted a case definition requiring only laboratory confirmation to define a confirmed case.[75] This laboratory-based definition of confirmed cases was unique to Arizona until 2018.[101] An interview study of laboratory-confirmed cases reported in 2007–2008 found that 95% met the clinical criteria of the national case definition.[75]

Lab A, a large commercial reference laboratory in Arizona, offers several serological tests for coccidioidomycosis including a panel with the *Coccidioides* enzyme immunoassay (EIA) and reflex to immunodiffusion and complement fixation, both of which are less sensitive and more specific tests. In June 2009, Lab A began reporting all positive EIA results without positive confirmatory test at the request of the state health department. Before this, Lab A only reported results for EIA IgM and/or IgG positive patients who were also positive by immunodiffusion and/or complement fixation. Other laboratories reported all positive results. In November of 2012, Lab A switched from the Premier *Coccidioides* EIA produced by Meridian Biosciences to the Omega *Coccidioides* antibody EIA produced by Immuno-Mycologics. Lab A continued to report EIA results without confirmatory tests after the test kit change. Case counts increased 129% between 2008 and 2009 and decreased 59% between 2012 and 2013. Concurrent with the 2009 change, the demographics of reported cases also shifted towards a higher proportion of female cases and lower mean age.

A multi-laboratory study of EIA reproducibility in which 150 cases and 50 controls were tested using the Meridian Biosciences and Immuno-Mycologics *Coccidioides* EIA kits at Lab A and two other reference laboratories found lower specificity and percent agreement with the Meridian Biosciences kit as performed at Lab A.[113] As Lab A most often performed tests as a serology panel, patients with false positive Meridian EIA results would then be tested by immunodiffusion and complement fixation. Thus, cases defined by EIA alone or combinations of EIA, immunodiffusion and/or complement fixation at Lab A between June 2009 and November 2012 might have been more likely to be false positive cases.

We adjusted reported case counts for potential biases associated with these surveillance changes and estimated bias-adjusted trends in reported coccidioidomycosis incidence in Arizona between 1998 and 2017.

Methods

We obtained records of laboratory-confirmed coccidioidomycosis between 1998 and 2017 from the state health department's communicable disease surveillance system. We restricted our analysis to the three largest counties in Arizona (Maricopa, Pima, and Pinal counties) where 80% of the state's population resides and 95% of reported coccidioidomycosis cases in the state occur.[97] To adjust for potential biases associated with the 2009 reporting change and the 2012 test kit change, we estimated two counterfactual scenarios: (1) case counts had Lab A not reported positive EIA results lacking confirmatory test results (i.e., case counts in the absence of the 2009 reporting change) and (2) reported case counts had Lab A used the Immuno-Mycologics EIA kit between the 2009 reporting change and the 2012 test kit change. Our goal was to create consistent time series for cases reported between 1998 and 2017 and between June 2009 (the reporting change) and 2017.

Missing and incomplete data due to evolving informatics systems and data collection practices complicate estimation of these counterfactuals for the entire period of interest. Between June 2009 and March 2011, laboratory test result and testing laboratory name was not consistently recorded and cannot be reliably identified for all cases (n=21,342). Between March 2011 and June 2012 (n=20,434 cases reported), testing laboratory information was not available for 6,463 (31.6%) cases, and laboratory test results could not be determined for 1,996 (9.8%) of cases. Data quality improved in later years with only 859 (2.3%) of 36,763 cases missing test result or testing laboratory information between June 2012 and December 2012.

For counterfactual scenario (1), we removed all cases that had positive EIA results performed at Lab A and no other positive *Coccidioides* laboratory test result (hereafter 'EIA positive only at Lab A'). However, this could not be determined for all cases due to the missing data problems summarized above. Thus, we imputed EIA positive only at Lab A status for cases with missing data using a multi-step process. First, we estimated the proportion of cases that were EIA positive only at Lab A within twelve demographic strata defined by case's county of residence, sex, and age (dichotomized at age 65 years). We then sampled from stratum-specific triangular distributions parameterized with the stratum-specific estimate and the lower and upper limits of the associated 95% confidence interval as the mode, minimum, and maximum, respectively. Finally, we performed a Bernoulli trial to determine whether each case was EIA positive only at Lab A using the stratum-specific proportion sampled in the previous step. As the prevalence of EIA positive only at Lab A status might have differed before and after the EIA test kit change, we calculated separate stratum-specific proportions from cases reported before and after the test kit change that had no missing data. For cases with known laboratory test results, but unknown testing laboratory, we estimated the probability of the testing laboratory being Lab A among EIA positive only cases. We similarly sampled this probability from a triangular distribution and then conducted a Bernoulli trial to determine EIA positive only at Lab A status. Cases with missing demographic information (n=497, 0.6%) were assumed to not be EIA positive only at Lab A.

For counterfactual scenario (2), we removed cases with positive test results from Lab A alone between June 2009 and November 2012 (i.e., when the Meridian test kit was in use) that would have tested negative using the Immuno-Mycologics assay. We estimated the proportion of Meridian EIA IgM positive only, EIA IgG positive only, EIA IgM and IgG positive only, and

EIA and immunodiffusion positive cases that had negative Immuno-Mycologics assay results using data from the previously mentioned multi-laboratory study reproducibility study.[113] Determination of laboratory test result pattern for cases with missing data also required imputation. We estimated stratum-specific proportions for each laboratory test result pattern and constructed and sampled from triangular distributions as described above. To assign one of five states (the four test result patterns or other) to each case with missing data, we constructed a stratum-specific categorical distribution based on the proportions drawn from the triangular distribution and then sampled from it. Cases missing testing laboratory information alone or demographic information were treated as above. The imputation procedure is detailed in Table 3-S1.

Sampling was repeated 10,000 times for each counterfactual scenario. For each simulation, we summed counts by year and calculated incidence rates and annual percent change in incidence rate. We also calculated the percent of cases that were male and the mean age in each simulation. These measures were summarized across simulations using medians and 95% uncertainty intervals (i.e., the range defined by the 2.5^{th} and 97.5^{th} percentiles). Separate analyses were performed for each county. Population denominators were obtained from the U.S. Census Bureau's county intercensal estimates.[140] All analyses were performed in SAS version 9.4 (SAS Institute, Cary, NC).

Results

There were 114,224 coccidioidomycosis cases reported in Maricopa, Pima, and Pinal counties between 1998 and 2017. Total annual case counts ranged from 1,451 in 1998 to 15,655 in 2011.The overall incidence rate ranged from 37.3 cases per 100,000 person-years in 1998 to 298.6 cases per 100,000 person-years in 2011. Cases counts were consistently highest in

Maricopa County, Arizona's most populous county. Although county-specific rates were more variable over time, annual rates were most often highest in Maricopa County, followed by Pinal County and Pima County, respectively. Rates for all three counties increased dramatically between 2008 and 2009 and decreased between 2012 and 2013 (Figure 3-1). Reported cases were predominantly male (range: 51–59%) before 2009. The percent of cases that were male declined between 2009 and 2012 (range: 47–48%) and then increased after 2012 (range: 50–54%). Mean age also varied by year and sex. Between 1998 and 2008, mean age ranged from 49 to 53 years and was higher among females. Mean age declined for both males and females between 2009 and 2012, but was higher among males. After 2012, mean age increased linearly for both sexes, reaching a maximum in 2017 (Figure 3-S2a).

The 2009 reporting change coincided with an immediate two- to three-fold increase in case counts for all counties (Figure 3-2a). The EIA test kit change occurred in late November 2012. In contrast to the 2009 report change, case counts decreased across all counties in subsequent weeks after the test kit change. The test kit change was also accompanied by a decline in the proportion of cases that were EIA IgM positive only at Lab A from an average of 41.7% in the 23 weeks prior to the change to an average of 12.8% in the remainder of the study period. However, changes of similar magnitude were not observed for the proportion EIA IgG positive only at Lab A (10.2% before vs. 16.6% after test kit change). Although a sharp decline in reported case counts was observed in late December and early January, the proportion EIA only at Lab A did not decline during this period (Figure 3-2b).

Demographic characteristics of reported cases by laboratory characteristics were available between June 2012 and December 2017. Demographic characteristics of cases that were EIA positive only at Lab A varied before and after the EIA test kit change (June 2012 and

November 2012 and December 2012 and December 2017, respectively). EIA positive only at Lab A cases were more likely to be residents of Pima County (9.5% vs. 12.3%) and Pinal County (6.7% vs. 8.6%) after the test kit change. The percentage male changed marginally (Appendix Table 3-S3). The relationship between EIA positive only at Lab A and age also varied across these two time period. Older cases were less likely to be EIA positive only at Lab A before the test kit change, but this relationship reversed after the test kit change (Figure 3-S1a).

Imputation parameters utilized in scenario (1) for cases with missing laboratory name and/or test result are summarized in Table 3-S4. Before the test kit change, EIA positive only cases were predominantly reported by Lab A (89%; 95% CI: 88%, 90%) and all of the key subtypes of EIA positive cases were also primarily reported by Lab A. Median and 95% uncertainty intervals of bias-adjusted case counts and rates for counterfactual scenario (1) are shown in Figure 3-3a. Counterfactual estimates for 2009–2017 were lower than observed values; 95% uncertainty intervals did not overlap with observed values for any county. Counterfactual rates were 20–59%, 15–38%, and 26–49% lower for Maricopa County, Pima County, and Pinal County, respectively. The magnitude of the adjustment was higher before the test kit change for all three counties. Consistent with observed rates, adjusted rates peaked in 2011 and then declined. However, adjusted rates were more similar across counties than observed rates. The observed average annual percent change in incidence rate was 12.3%, 8.8%, and 8.8% for Maricopa County, Pima County, and Pinal County, respectively. The bias-adjusted average annual percent change in incidence was 7.8% (95% UI: 7.7%, 7.9%), 6.5% (95% UI: 6.4%, 6.5%), and 5.4% (95% UI: 5.0%, 6.1%) for Maricopa County, Pima County, and Pinal County, respectively. Counterfactual estimates of annual demographic characteristics were substantially different from observed values. The mean bias-adjusted percentage male cases was 14.6% higher

between 2009 and 2017 than observed. The bias-adjusted mean age was higher than the observed mean age between 2009 and 2013, but lower in 2014, 2015, and 2017 (Figure 3-S2a).

Imputation parameters utilized in scenario (2) for cases with missing laboratory name and/or test result are summarized in Tables 3-S5 and 3-S6. Median and 95% uncertainty intervals of bias-adjusted case counts and rates for counterfactual scenario (2) are shown in Figure 3-3b. Counterfactual estimates for 2009–2012 were also lower than observed values. While 95% uncertainty intervals did not overlap with observed values, intervals were wider than estimates from counterfactual scenario (1), reflecting greater uncertainty. Counterfactual rates were 37% to 47%, 25% to 37%, and 37% to 47% lower for Maricopa County, Pima County, and Pinal County, respectively. Consistent with observed rates and counterfactual scenario (1), adjusted rates peaked in 2011 and then declined with the exception of Pinal County for which the adjusted 2011 rate was similar to the observed 2017 rate (120.9 in 2011 and 121.0 in 2017). The observed average annual percent change in incidence rates between 2011 and 2017 was -4.2%, -2.7%, and 1.8% for Maricopa County, Pima County, and Pinal County, respectively. The bias-adjusted average annual percent change in incidence was -1.8%, 0.3%, and 5.6% for Maricopa County, Pima County, and Pinal County, respectively; however, uncertainty intervals for these estimates included zero. Unlike counterfactual scenario (1), the counterfactual estimates of annual demographic characteristics for scenario (2) were only marginally different from observed values. The bias-adjusted percent of male cases was 1.7% to 2.8% higher than the observed values between 2010 and 2012. The bias-adjusted mean age was higher than the observed mean age between 2010 and 2012, although 95% uncertainty intervals overlapped with observed values (Figure 3-2b).

Discussion

We estimated bias-adjusted trends in reported coccidioidomycosis incidence in the three largest Arizona counties, where a majority of coccidioidomycosis cases occur. Accurate trend estimates require consistent surveillance, which we approximated by using probabilistic removal of cases that would not have been reporting (1) if the 2009 reporting change had not occurred and (2) if Lab A had used the IMMY EIA kit between 2009 and 2017. Bias-adjusted counts of reported coccidioidomycosis cases in these three counties were substantially lower than observed case counts in both counterfactual scenarios. While the degree of adjustment varied by scenario, year, and county, we found that neither surveillance change altered the overall directions of observed trends in reported coccidioidomycosis incidence. Thus, we provide further evidence that rates of reported coccidioidomycosis increased between 1998 and 2017.

After adjustment for the 2009 reporting change, the bias-adjusted average annual percent change in incidence rate between 1998 and 2017 ranged from 5.4% to 7.8%, indicating increasing incidence. Bias-adjusted rates between 2009 and 2012 were elevated, and record high rates of reported cases in 2011 persisted after bias adjustment. However, the large observed increase in reported cases in 2015 was not seen across all counties in the bias-adjusted time series. Cases reported during this particular increase might have been disproportionately EIA positive only at Lab A. While the 2011 peak might be associated with natural phenomena (e.g., fungal activity), the inconsistency of the 2015 increase across counties alludes to a different mechanism, perhaps related to testing or careseeking. Adjusting for the 2012 test kit change also attenuated rates between 2010 and 2012. Notably, there was considerably more uncertainty in the bias-adjusted 2010–2017 time series than the 1998–2017 series due to the imprecise bias parameter estimates used in the former analysis. Differences in the effect of adjustment across

counties might reflect Lab A's market share and catchment areas during the period in question rather than differences in patient or case characteristics.

Adjustment for surveillance changes also affected the demographic composition of reported cases. Adjustment for the 2009 reporting change substantially increased the proportion of male cases and the mean age. There were only minor differences in case demographics after adjustment for the 2012 test kit change. This suggests that use of the Meridian EIA test kit at Lab A was associated with more positive test results among younger and female patients. The mechanisms behind these associations between EIA positive only at Lab A and age and sex are unclear and require further exploration. The Meridian test kit had higher sensitivity and lower specificity than the IMMY kit as performed at Lab A[113], but it is unknown whether test kit performance differ by sex and age. While male sex is associated with severe coccidioidomycosis[28], whether antibody levels and kinetics vary by sex is unknown. Age alone does not appear to be associated with severity of disease after adjustment for comorbidities.[71] A simpler explanation could be that tested younger or female patients are less likely to have coccidioidomycosis than tested older or male patients; a test with lower specificity would thus generate more false positive results among younger or female patients and consequently alter the demographics of reported cases as observed. Future studies should use reference laboratory data to compare the demographics of patients who tested EIA negative vs. positive with either test kit to support or refute this hypothesis.

We could not address some possible effects of the 2009 reporting change. Simultaneous with the change in reporting to the state health department, Lab A began reporting all positive EIA results to providers with a statement stating that isolated positive EIA results should be confirmed by immunodiffusion. Before this change, providers were shown a negative

interpretation if the EIA test was negative or the EIA test was positive and the reflex immunodiffusion test was negative and a positive interpretation when both the EIA test and reflex immunodiffusion tests were positive. The impact of this change on healthcare provider behavior (e.g., the likelihood of a future patient being tested) is unknown. Before the 2009 reporting change, Lab A used an alternative cut-off value to interpret the Meridian Biosciences EIA test. An absorbance value of 0.150 or higher was reflexed to testing with the immunodiffusion and complement fixation tests. Meridian Biosciences defines an absorbance value of less than 0.150 as negative, 0.150 to 0.199 as indeterminate, and 0.200 as positive. Simultaneous with the 2009 reporting change, Lab A raised the threshold for reflex to further testing to 0.200; this is consistent with the manufacturer's interpretation guidance. Thus, more patients were likely tested with the immunodiffusion and complement fixation tests before the 2009 reporting change. Finally, our adjustment for the 2012 test kit change relied upon a multi-laboratory validation study of the Meridian and IMMY EIA test kits using serum from 50 controls (CDC employees from a non-endemic area) and 150 cases from Kern County, California, another highly endemic area. It is possible that these cases and controls might not be representative of patients tested in these three counties between 2009 and 2012.

Our study highlights the tension between increasing the sensitivity of coccidioidomycosis surveillance and maintaining consistency for trend analysis. Improved case ascertainment would yield more accurate estimates of disease burden. Yet this analysis necessarily underestimates the true incidence of coccidioidomycosis in Arizona: an unknown proportion of removed cases likely had coccidioidomycosis and would have met the CSTE case definition for coccidioidomycosis. While some reports[43,106,107] cast doubt on the specificity of the EIA, particularly isolated IgM positive results, several studies have found excellent

specificity[41,102,103,108,109,111] and lower than expected sensitivity.[112,113] Overall, studies of the EIA's performance are difficult to interpret because of differences in testing laboratory, clinical characteristics of included patients, prevalence of disease in the study population, reasons for testing, use of endemic vs. non-endemic control sera, timing of testing in relation to the serologic response, and the lack of a clear diagnostic gold standard.

New and emerging diagnostics for coccidioidomycosis such as the recently introduced lateral flow assay[141] are likely to affect the sensitivity and specificity of surveillance. Public health agencies can anticipate and prepare for these changes by planning to conduct studies to assess their impact and estimate bias parameters to maintain consistent time series of reported case counts. The introduction of novel diagnostic tests and changes in surveillance are not unique to coccidioidomycosis. Increased use of culture-independent assays for enteric[142] and respiratory pathogens and modernization of public health informatics infrastructure poses challenges for infectious disease surveillance in the U.S. Our analysis provides a case study for the application of flexible methods to adjust time series of other reportable conditions for changes in testing and reporting in the setting of missing data.

Figure 3-1. Reported coccidioidomycosis case counts and rates by county, 1998–2017

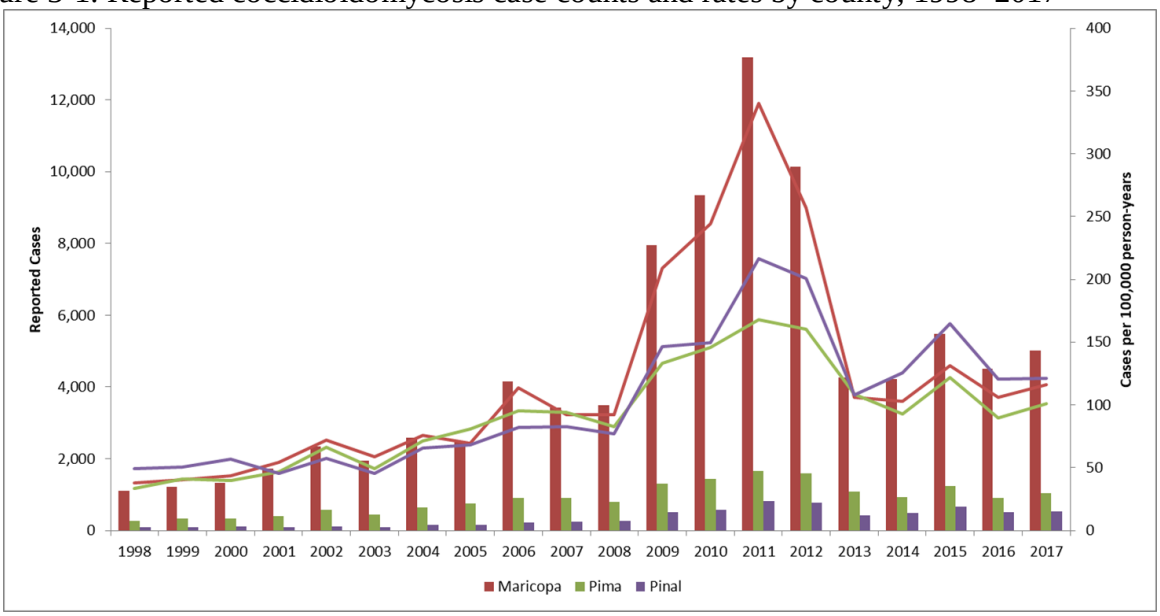


Figure 3-2a. Weekly reported coccidioidomycosis before and after Lab A reporting change by county, March–August 2009

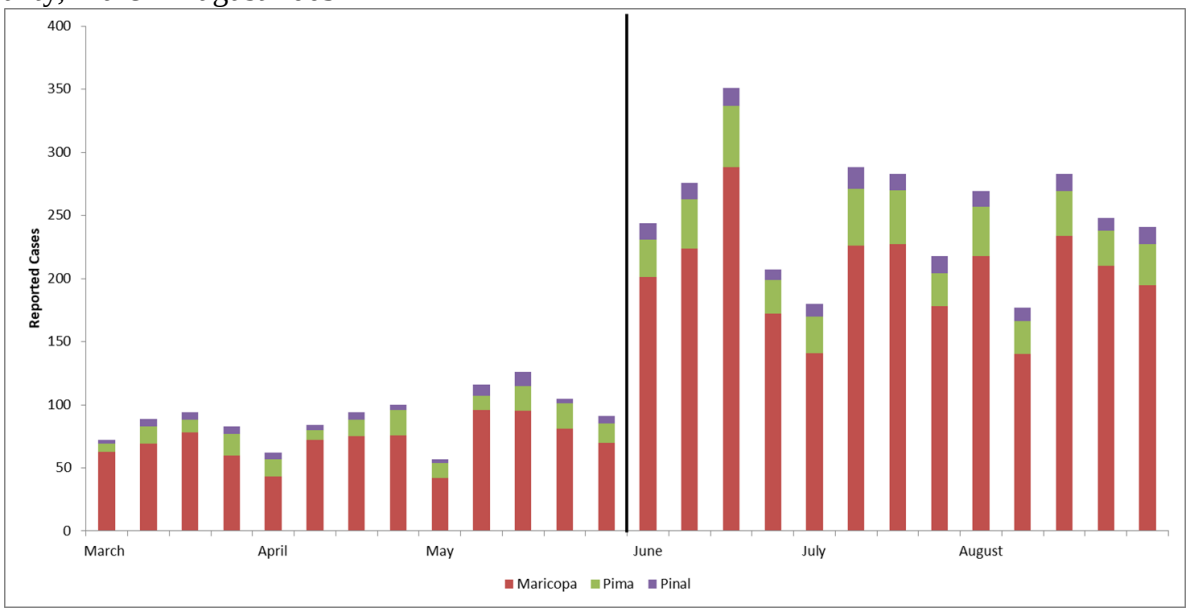
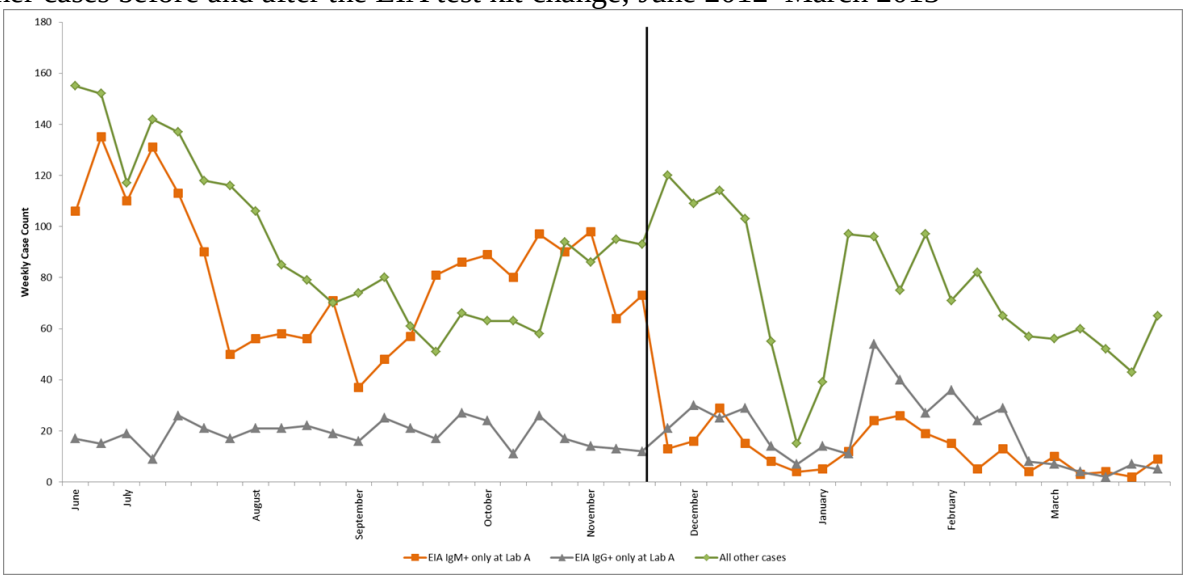


Figure 3-2b. Weekly reported count of EIA IgM+ only at Lab A, EIA IgG+ only at Lab A, and other cases before and after the EIA test kit change, June 2012–March 2013



*Black line indicates surveillance change

Figure 3-3a. Crude and median bias-adjusted rates and 95% uncertainty intervals by county -- Counterfactual (1)

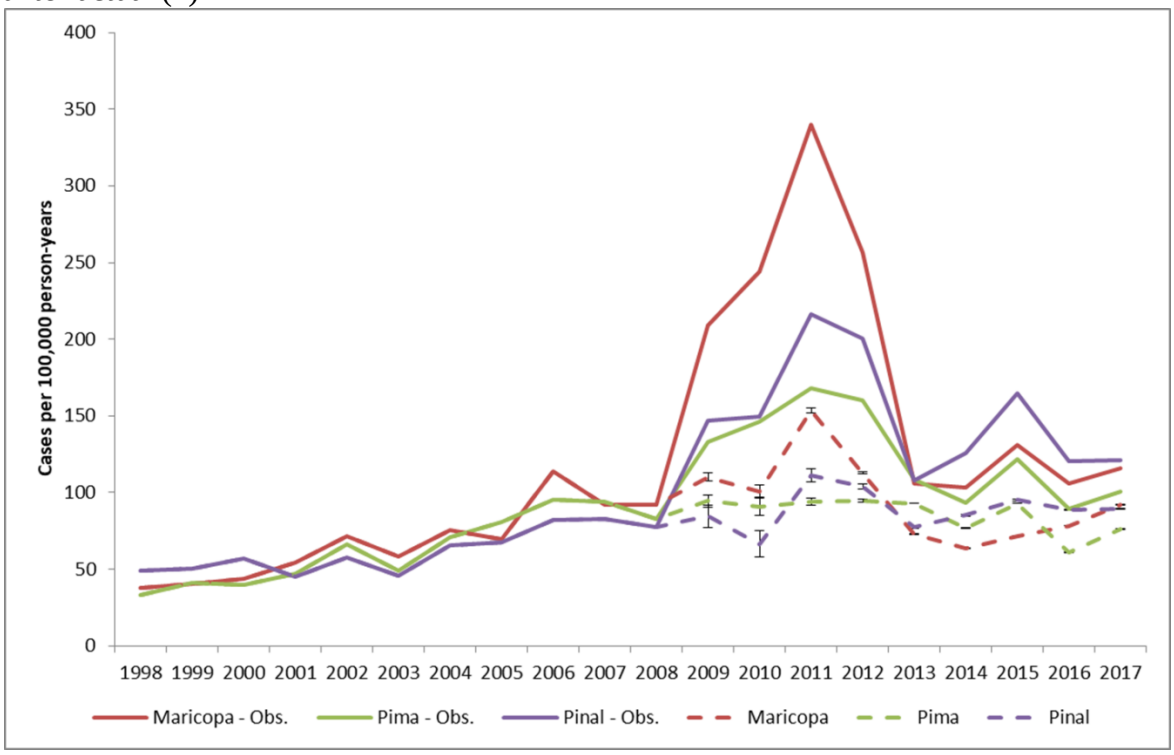


Figure 3-3b. Crude and median bias-adjusted rates and 95% uncertainty intervals by county -- Counterfactual (2)

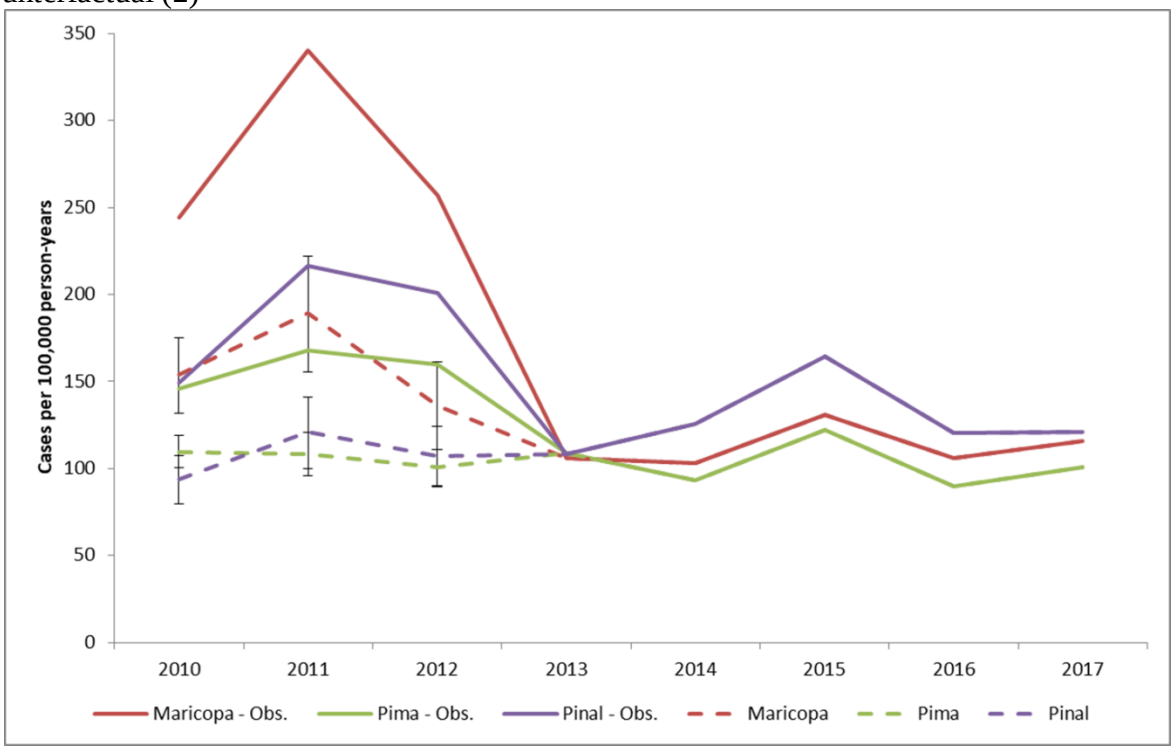


Figure 3-S1a. Percent EIA+ only at Lab A by age: Before EIA test kit change (June 2012–November 2012)

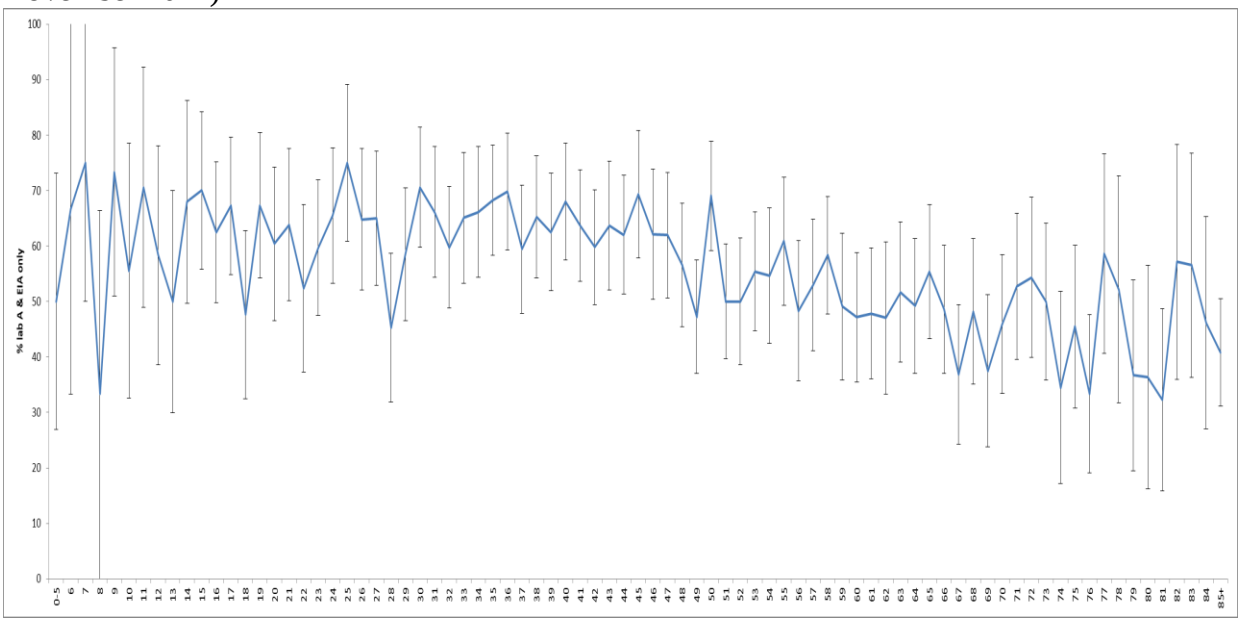


Figure 3-S1b. Percent EIA+ only at Lab A by age: Before EIA test kit change (November 2012–December 2017)

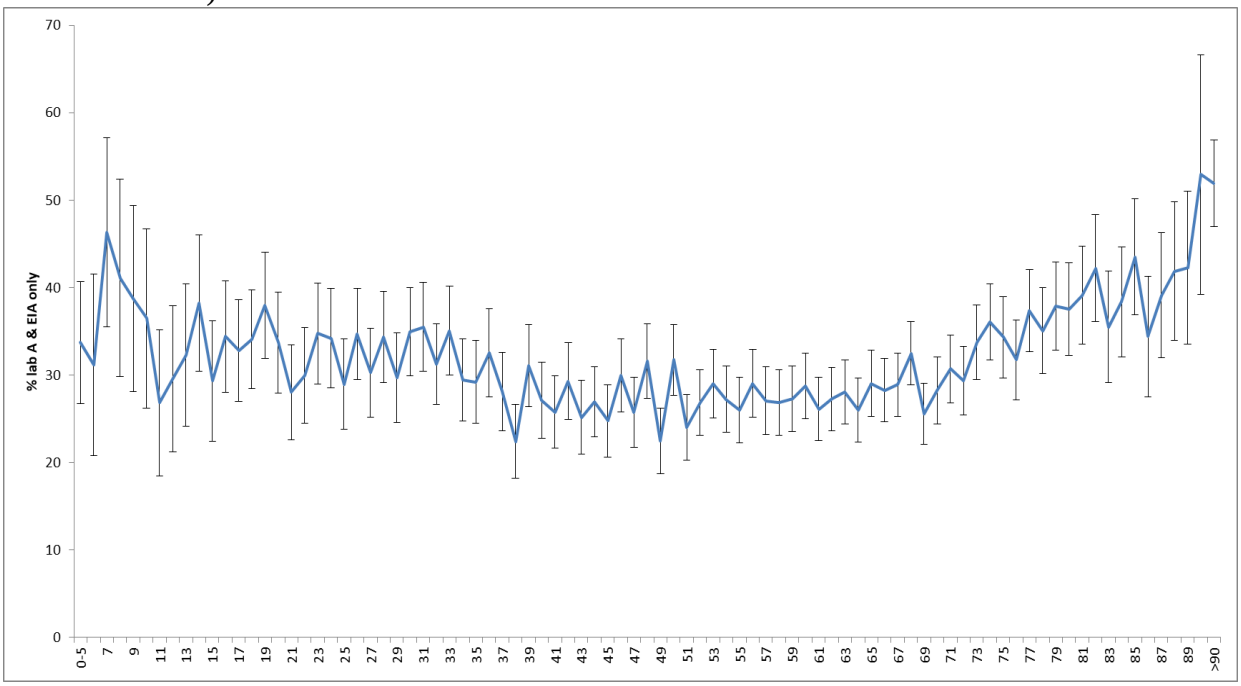


Figure 3-S2a. Crude and median bias-adjusted mean age and percent male, 1998-2017 - Counterfactual (1)

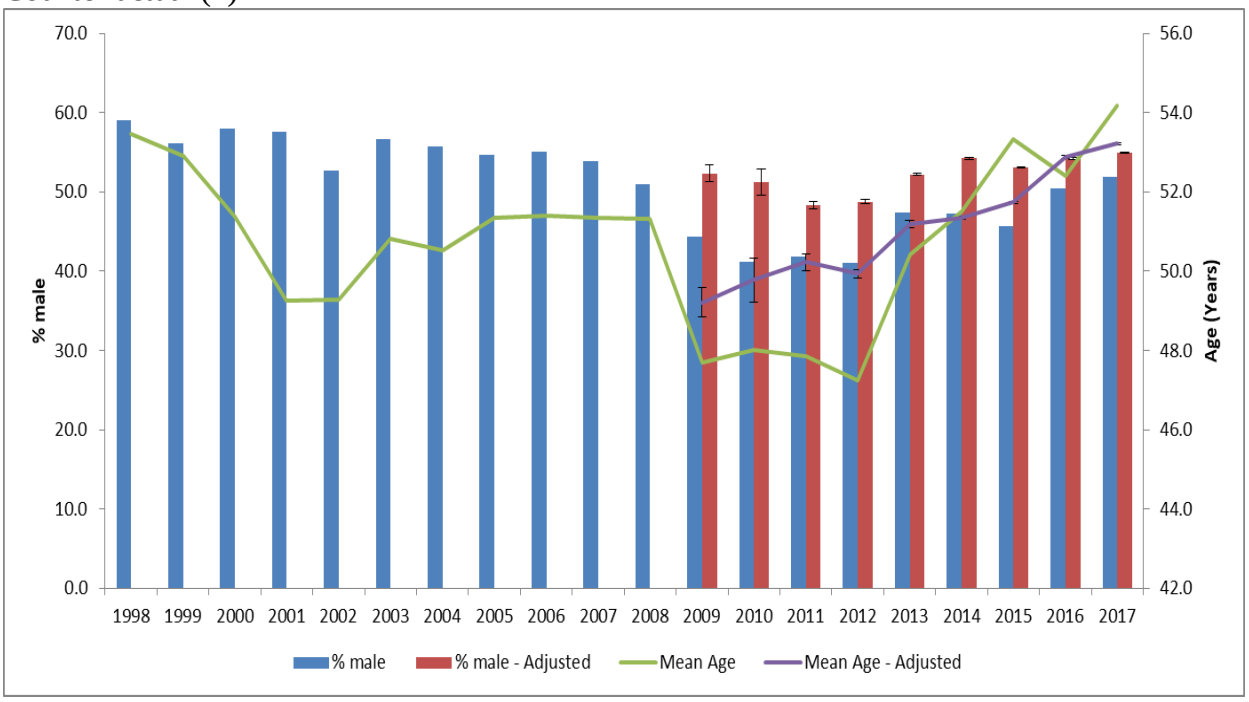


Figure 3-S2b. Crude and median bias-adjusted mean age and percent male, 2010–2017- Counterfactual (2)

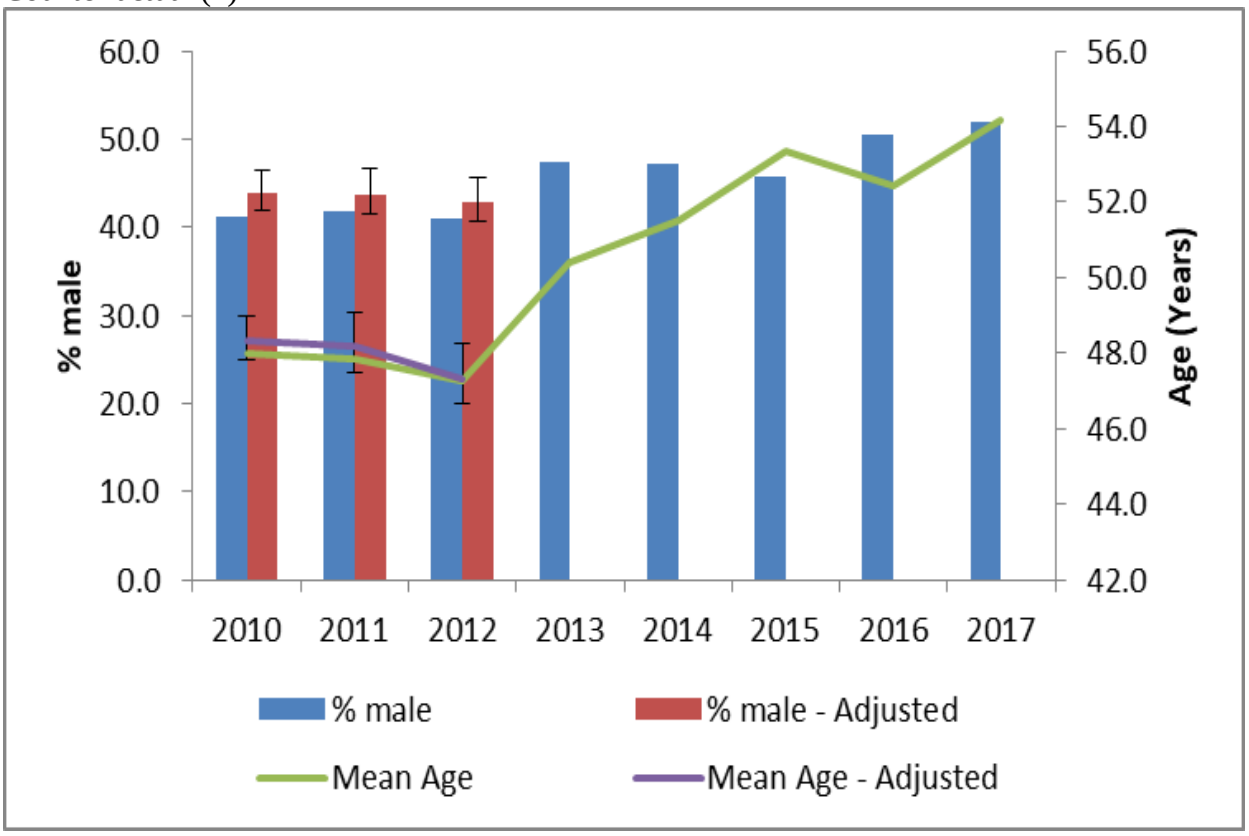


Table 3-S1. Missing data and imputation strategies by time period and analysis

Time Period	**N**	**Missing Data**	**Counterfactual (1) Imputation Strategy**	**Counterfactual (2) Imputation Strategy**
June 2009 – February 2011	21,342	Test result and testing laboratory information are missing for all cases. Demographic data are missing for 389 (1.8%) cases.	1. Using June 2012 – November 2012 cases with no missing data, estimate p(lab A & EIA+ only) by county, age, and gender stratum and 95% confidence interval 2. Draw stratum-specific p(lab A & EIA+ only) from a triangular distribution with the estimate from (1), lower limit of the confidence interval, and upper limit of the confidence interval as mode, minimum and maximum, respectively. 3. Assign lab A & EIA+ only status to each case using a Bernoulli distribution parameterized with the value drawn in (2).	1. Using June 2012 – November 2012 cases with no missing data, estimate five parameters [p(lab A & EIA+ IgM only), p(lab A & EIA+ IgG only), p(lab A & EIA+ IgM and IgG only), p(lab A & EIA and immunodiffusion+ only), p(other test result pattern)] by county, age, and gender stratum and 95% confidence interval 2. Draw stratum-specific parameters from a triangular distribution with the estimate from (1), lower limit of the confidence interval, and upper limit of the confidence interval as mode, minimum and maximum, respectively. 3. Sum values drawn from (2). Create proper probabilities from values drawn from (2) by dividing each value by the calculated sum. Assign test result pattern status to each case using a categorical distribution parameterized with the probabilities calculated in (3).
March 2011 – June 2012	20,434	Testing laboratory information is missing for 6,463 (31.6%) cases with a test result pattern of interest. Test result and	For cases missing testing laboratory only: 1. Using June 2012 – November 2012 cases with no missing data, estimate p(lab A|EIA+ only) and 95% confidence interval.	For cases missing testing laboratory only: 1.Using June 2012 – November 2012 cases with no missing data, estimate p(lab A|test result pattern) and 95%

		testing laboratory information is missing for 1,996 (9.8%) cases. Demographic data are missing for 108 (0.5%) cases.	2. Draw p(lab A|EIA+ only) from a triangular distribution with the estimate from (1), lower limit of the confidence interval, and upper limit of the confidence interval as mode, minimum and maximum, respectively. 3. Assign lab A status to each EIA+ only case using a Bernoulli distribution parameterized with the value drawn in (2). For cases missing test result and testing laboratory information, apply the same strategy as June 2009–February 2011.	confidence intervals. 2.Draw p(lab A|test result pattern) from a triangular distribution with the estimate from (1), lower limit of the confidence interval, and upper limit of the confidence interval as mode, minimum and maximum, respectively. 3.Assign lab A status to each case with the corresponding test result pattern using a Bernoulli distribution parameterized with the value drawn in (2). For cases missing test result and testing laboratory information, apply the same strategy as June 2009-February 2011.
June 2012 – December 2017	36,763	Test result and testing laboratory information are missing for 859 (2.3%) cases. No missing demographic data.	If the case was reported before November 2012 test kit change, apply the same strategy as June 2009–February 2011. If the case was reported after the test kit change, apply the same strategy as above except estimate p(lab A & EIA+ only) by county, age, and gender stratum using November 2012 – December 2017 cases with no missing data.	If the case was reported before November 2012 test kit change, apply the same strategy as June 2009-February 2011. If the case was reported after the test kit change, apply the same strategy as above except estimate the five parameters by county, age, and gender stratum using November 2012 – December 2017 cases with no missing data.

Table 3-S2. Bias parameter estimates from multi-laboratory study of *Coccidioides* EIA reproducibility[113]

Test Result Pattern	Total (n)	% negative on IMMY assay	
		n (%)	95% CI
Meridian EIA IgM and IgG positive	13	9 (69%)	(44%, 94%)
Meridian EIA IgM positive only	15	8 (53%)	(28%, 79%)
Meridian EIA IgG positive only	12	12 (100%)	(73%, 100%)
Meridian EIA and immunodiffusion positive	43	7 (16%)	(7%, 31%)
Meridian EIA and complement fixation positive	1	0 (0%)	--
Meridian EIA, immunodiffusion, and complement fixation positive	47	1 (2%)	(0%, 11%)

Table 3-S3. Demographics of EIA+ only at Lab A before and after EIA test kit change

	Before EIA test kit change (June 2012-November 2012) N=4,372	**After EIA test kit change (November 2012-December 2017) N=31,215**
	EIA+ only at Lab A N=2,476 (56.6%)	EIA+ only at Lab A N=9,604 (30.8%)
Male	825 (33.3%)	3,519 (36.6%)
County of residence		
Maricopa	2,073 (83.7%)	7,590 (79.0%)
Pima	236 (9.5%)	1,184 (12.3%)
Pina	167 (6.7%)	830 (8.6%)

Table 3-S4. Demographic stratum-specific prevalence of EIA only at Lab A before and after EIA test kit change

Stratum	P(Lab A & EIA+ only)	
	Before EIA test kit change	After EIA test kit change
Maricopa, female, age <65	0.70 (0.68, 0.72)	0.38 (0.37, 0.40)
Maricopa, female, age ≥ 65	0.57 (0.52, 0.62)	0.45 (0.43, 0.46)
Maricopa, male, age < 65	0.51 (0.48, 0.54)	0.21 (0.20, 0.22)
Maricopa, male, age ≥ 65	0.42 (0.36, 0.47)	0.31 (0.29, 0.33)

Pima, female, age <65	0.51 (0.45, 0.57)	0.27 (0.25, 0.29)
Pima, female, age ≥ 65	0.41 (0.29, 0.53)	0.24 (0.21, 0.27)
Pima, male, age < 65	0.31 (0.25, 0.38)	0.20 (0.18, 0.22)
Pima, male, age ≥ 65	0.13 (0.06, 0.20)	0.16 (0.14, 0.19)
Pinal, female, age <65	0.76 (0.69, 0.84)	0.40 (0.37, 0.43)
Pinal, female, age ≥ 65	0.47 (0.30, 0.64)	0.39 (0.34, 0.44)
Pinal, male, age < 65	0.39 (0.29, 0.49)	0.23 (0.20, 0.25)
Pinal, male, age ≥ 65	0.46 (0.30, 0.62)	0.27 (0.23, 0.31)

Table 3-S5. Demographic stratum-specific test result pattern prevalence, June 2012–November 2012

Stratum	**P(Lab A & EIA IgM+ only) (95% CI)**	**P(Lab A & EIA IgG+ only) (95% CI)**
Maricopa, female, age < 65	0.60 (0.58, 0.63)	0.06 (0.05, 0.07)
Maricopa, female, age ≥ 65	0.33 (0.28, 0.38)	0.19 (0.15, 0.22)
Maricopa, male, age < 65	0.35 (0.32, 0.38)	0.11 (0.09, 0.13)
Maricopa, male, age ≥ 65	0.18 (0.13, 0.22)	0.20 (0.15, 0.24)
Pima, female, age <65	0.41 (0.35, 0.46)	0.06 (0.03, 0.09)
Pima, female, age ≥ 65	0.29 (0.17, 0.40)	0.11 (0.03, 0.19)
Pima, male, age < 65	0.19 (0.13, 0.25)	0.08 (0.04, 0.11)
Pima, male, age ≥ 65	0.06 (0.01, 0.11)	0.06 (0.01, 0.11)
Pinal, female, age <65	0.61 (0.52, 0.69)	0.10 (0.05, 0.16)
Pinal, female, age ≥ 65	0.34 (0.18, 0.51)	0.09 (0, 0.19)
Pinal, male, age < 65	0.24 (0.16, 0.33)	0.10 (0.04, 0.16)
Pinal, male, age ≥ 65	0.18 (0.06, 0.3)	0.21 (0.08, 0.33)

Stratum	**P(Lab A & EIA IgM/IgG+ only) (95% CI)**	**P(Lab A & EIA/immunodiffusion+ only) (95% CI)**
Maricopa, female, age < 65	0.036 (0.03, 0.045)	0.05 (0.04, 0.06)
Maricopa, female, age ≥ 65	0.05 (0.03, 0.07)	0.06 (0.04, 0.09)
Maricopa, male, age < 65	0.05 (0.03, 0.06)	0.11 (0.09, 0.13)
Maricopa, male, age ≥ 65	0.04 (0.02, 0.06)	0.11 (0.07, 0.14)
Pima, female, age <65	0.05 (0.02, 0.07)	0.11 (0.07, 0.14)
Pima, female, age ≥ 65	0.02 (0, 0.05)	0.06 (0, 0.12)
Pima, male, age < 65	0.05 (0.02, 0.08)	0.08 (0.04, 0.12)
Pima, male, age ≥ 65	0 --	0.08 (0.02, 0.13)
Pinal, female, age <65	0.06 (0.02, 0.09)	0.07 (0.03, 0.12)
Pinal, female, age ≥ 65	0.03 (0, 0.09)	0.19 (0.05, 0.32)
Pinal, male, age < 65	0.05 (0.01, 0.10)	0.18 (0.10, 0.26)

Pinal, male, age ≥ 65	0.08 (0, 0.16)	0.15 (0.04, 0.27)

Stratum	P(other) (95% CI)
Maricopa, female, age < 65	0.25 (0.23, 0.27)
Maricopa, female, age ≥ 65	0.37 (0.32, 0.42)
Maricopa, male, age < 65	0.38 (0.35, 0.41)
Maricopa, male, age ≥ 65	0.47 (0.42, 0.53)
Pima, female, age <65	0.38 (0.32, 0.44)
Pima, female, age ≥ 65	0.52 (0.40, 0.65)
Pima, male, age < 65	0.61 (0.53, 0.68)
Pima, male, age ≥ 65	0.80 (0.71, 0.88)
Pinal, female, age <65	0.17 (0.10, 0.23)
Pinal, female, age ≥ 65	0.34 (0.18, 0.51)
Pinal, male, age < 65	0.43 (0.33, 0.53)
Pinal, male, age ≥ 65	0.38 (0.23, 0.54)

Table 3-S6. Probability lab A was the testing laboratory given test result pattern, June 2012–November 2012

Test Result Pattern	Estimate (95% CI)
EIA IgM+ only	0.92 (0.90, 0.93)
EIA IgG+ only	0.83 (0.79, 0.86)
EIA IgM/IgG+ only	0.79 (0.73, 0.84)
EIA/immunodiffusion + only	1 (0.99, 1)

CHAPTER 4: METHODOLOGICAL ISSUES IN UNDERSTANDING THE RELATIONSHIP BETWEEN WEATHER AND COCCIDIOIDOMYCOSIS INCIDENCE IN ARIZONA

Background

Coccidioidomycosis is an infectious disease caused by *Coccidioides* species, fungi found in the southwestern United States and other desert regions of the Americas.[1] Inhalation of spores produced by these organisms results in infection ranging in severity from asymptomatic to lethal disseminated disease.[2] Nearly two-thirds of all cases reported between 1998 and 2017 in the United States occurred in Arizona. Rates of reported disease increased five-fold during this time period.[45] In addition to this long-term trend, annual epidemics of coccidioidomycosis display distinct seasonality and vary dramatically in magnitude. Though the causes of these patterns are unclear, weather is frequently cited as a driver of coccidioidomycosis incidence.[143]

Our understanding of the behavior of these organisms in the environment is limited. Climate has long been thought to govern *Coccidioides* growth and dispersal of spores. This is supported by the biology and distribution of these organisms. Factors hypothesized to affect the fungus include precipitation, temperature, relative humidity, dust storms, soil characteristics (moisture, salinity and concentration of other trace elements, organic matter, pH), competing soil microbes, small mammal activity, vegetation, and the presence of desert washes and stream beds or banks.[8] Water plays a central role in the lifecycle of *Coccidioides* as moisture is required for the fungus to grow. However, their presence appears to be exclusive to deserts, suggesting that hot summers and mild winters might also be necessary for fungal growth and propagation.[8,117]

A link to climate is also supported by the seasonality of human infections, which has been observed in Arizona since the 1950s.[55] This seasonality motivates quantitative studies of the relationship between weather and the incidence of reported coccidioidomycosis in Arizona. Numerous studies have found associations of varying magnitudes between precipitation,

temperature, concentration of airborne particles 2.5–10 microns in diameter (PM_{10}), dust storm frequency, soil moisture, and incidence. While the timing and magnitude of effects are inconsistent across studies, several studies point to a relationship between lagged precipitation (or soil moisture), temperature, and incidence.[120]

Studies to date have primarily sought to understand the ecological relationship between weather and *Coccidioides* growth and dispersal using human cases as an indirect measure of fungal activity.[8,119] Results are difficult to interpret across studies due to methodological differences including temporal aggregation (e.g., month vs. season) and the subjective nature of the variable selection process for multivariable modeling. For example, associations with precipitation at lags between four months and three years have been reported in the literature. Moreover, reported incidence data are complicated by changes in changes in public health surveillance for coccidioidomycosis, which are mostly unaddressed by the literature, and heterogeneity of disease presentation. Finally, model evaluation in published studies focused on the proportion of variance explained (i.e., R^2) or n-fold cross-validated error, neither of which resemble how a useful predictive model would be prospectively implemented and tested in practice.

We developed models of weather and coccidioidomycosis incidence in two Arizona counties and attempted to address key methodological issues arising in modeling the relationships between weather and coccidioidomycosis.

Methods

We obtained monthly counts of coccidioidomycosis cases reported to the Arizona Department of Health Services between 1998 and 2017 among Maricopa County and Pima County residents. We restricted our analysis to Maricopa County and Pima County because data

on environmental variables were consistently available for these areas and previous studies found differing seasonality of incidence by county.[120] Together, these two jurisdictions account for 80% of the state's population and 95% of reported coccidioidomycosis cases during this timeframe. Changes in laboratory reporting and testing practices have substantially influenced case counts between 2009 and 2017 (Chapter 3). To create a consistent time series for analysis, we adjusted June 2009 through 2017 weekly counts by removing cases that would not have been reported in the reporting scheme that was in place between 1998 and May 2009. We could not identify all of these cases with certainty due to missing data. Thus, we used Monte Carlo simulation to probabilistically remove cases based on their demographic characteristics and reporting timeframe and estimated the mean weekly bias-adjusted case count from 10,000 simulations. These methods and results have been described elsewhere (Chapter 3). County population denominators were obtained from the U.S. Census Bureau's intercensal estimates and used to calculate monthly incidence rates in person-months.[140]

Environmental variables include total precipitation (centimeters), average air temperature (degrees Celsius), average wind speed (meters/second), average wind vector direction (degree), and concentration of airborne particles 2.5–10 microns in diameter (PM_{10}; micrograms/m^3). Weather data were obtained from the Arizona Meteorological Network.[144] PM_{10} data were obtained from the Environmental Protection Agency.[145] For all variables, we only included stations in the study area that were continuously active between 1996 and 2017 and averaged daily measures across stations to compute a monthly mean (or sum in the case of total precipitation). Invalid (e.g., implausible or flagged values) daily measures were discarded.

We described the distributions of incidence rates and environmental variables using descriptive statistics, graphical methods (e.g., time series plots and box-and-whisker plots),

autocorrelation analysis, and additive seasonal and trend decomposition using LOESS.[146] We then examined relationships between environmental variables and monthly incidence rate in each county using multiple methods. To describe concurrent and lagged relationships, we calculated and plotted cross-correlation functions between incidence and each environmental variable. We then constructed bivariate Pearson correlation coefficient heat maps by calendar month to identify more complex lagged relationships. We used these results to guide the creation of additional variables to summarize incidence-weather relationships (e.g., average of previous year December and January total precipitation) and calculated Pearson correlation coefficients for these composite variables as well. Finally, we examined whether different factors affected the seasonality of incidence rate and/or interannual variation in incidence. We used additive seasonal and trend decomposition using LOESS with a 12-month smoothing window and plotted (i) the seasonal cycle of incidence and each environmental factor and (ii) the seasonally-adjusted trends in incidence and each environmental factor.

We incorporated several analyses to explore and address methodological issues:

- Temporal aggregation of incidence – We compared results from bivariate analyses using monthly vs. meteorological seasonal average incidence rate.
- Changes in surveillance – We compared results from descriptive and bivariate analyses using the unadjusted vs. adjusted monthly incidence rate.
- Heterogeneity among reported cases – As reported cases are heterogeneous with respect to time between exposure and positive laboratory test report, we repeated the bivariate analysis using counts of cases aged 65 years and older only. This age group might be more homogeneous with respect to access to healthcare due to Medicare and prevalence of

comorbidities, both likely determinants of timing of careseeking and probability of being tested, and has the highest age group-specific incidence rate in Arizona.

For multivariable models, we selected predictors based on the magnitude of correlation with incidence rate and consistency of lagged relationships across the abovementioned exploratory methods. We modeled the log of the monthly incidence rate using linear regression. Model evaluation was based on cross-validated performance. To simulate prospective runs of prediction models, we used rolling origin cross-validation. This method has been suggested for evaluating forecasting models of time series.[146] The procedure for cross-validation was as follows: for the one-month horizon prediction models, (1) train a model based on 1998–2002 case counts, (2) predict January 2003 incidence and (3) compare to observed incidence to calculate performance metrics. This was process was repeated by 'rolling' forward in time: training using 1998–January 2003 observed case counts, prediction of February 2003 incidence, and so on. We report performance metrics averaged across all one-step-ahead predictions. Model covariates also included time (months since January 1998) and calendar month. Metrics for assessment of model performance included root mean squared error, mean absolute error, and mean absolute percentage error.

All analyses were conducted separately for Maricopa County and Pima County. Analyses were conducted in SAS version 9.4 (SAS Institute, Cary, NC) and R version 3.5.2.[147]

Results

There were 89,822 and 17,523 cases reported between 1998 and 2017 in Maricopa and Pima counties, respectively. To create a consistent time series, we removed cases that would have not have been reported prior to June 2009. These cases were only *Coccidioides* enzyme immunoassay positive at a major commercial laboratory and lacked additional positive test

results. After bias adjustment for this surveillance change, 60,073 and 14,076 cases remained for each county. Of these, 16,014 (26.7%) and 4,179 (29.7%) were aged 65 years and older. In Maricopa County, unadjusted monthly incidence rates ranged from 0.89 cases per 100,000 person-months to 35.6 cases per 100,000 person-months with a mean and median of 9.84 and 7.46, respectively. Adjusted rates were lower (mean: 6.69 cases per 100,000 person-months) and less variable (standard deviation: 3.22 vs. 7.50) than unadjusted rates. Adjusted rates for persons 65 years and older were higher (mean: 14.47) than overall unadjusted and adjusted rates. Monthly rates were lower in Pima County; unadjusted monthly incidence rates ranged from 0.81 cases per 100,000 person-months to 20.34 cases per 100,000 person-months with a mean and median of 7.59 and 4.05, respectively. Adjusted rates were also lower (mean: 6.15 cases per 100,000 person-months) and less variable (standard deviation: 2.66 vs. 4.05). Adjusted rates for persons 65 years and older were also higher (mean: 11.48) than overall unadjusted and adjusted rates (Table 4-1).

Unadjusted monthly rates increased linearly until 2009 after which rates increased dramatically and were elevated through 2012. Bias-adjusted rates had similar trends, although 2009–2012 rates were lower compared to unadjusted rates. Rates declined in 2012. Seasonality of monthly incidence rates differed between counties. In both counties, mean monthly incidence rates were highest in winter and lowest in spring, with a much smaller peak in late summer. However, peak Pima County rates were similar while in Maricopa County the winter peak was substantially higher than the summer peak. For both counties, December incidence rates were more variable than other months. In Maricopa County alone, 2009–2012 seasonality differed from other years, even after adjustment for surveillance changes. Overall, seasonality did not differ substantially between the adjusted and unadjusted series. Additive seasonal and trend

decomposition using LOESS supported these observations regarding long-term trends and seasonality.

Autocorrelation and partial autocorrelation functions of up to 24-month lags provided further evidence of an annual seasonal cycle and differences across counties, with moderate differences before and after adjustment. For Maricopa County, there was strong first-order autocorrelation (0.70) and weaker autocorrelation with observations 11 to 12 months prior (0.24 and 0.17) for the adjusted time series. In the unadjusted series, the strength of first-order autocorrelation was greater (0.88), stronger second-order autocorrelation (0.32 vs. 0.14) and similar autocorrelation with observations 11 to 12 months prior (0.22 and 0.06). For Pima County, first-order autocorrelation was moderate (0.52), and there was weak autocorrelation at other lags (two, five, 11, and 12). The unadjusted series had stronger autocorrelation at similar lags. Weak negative autocorrelation (-0.18 and -0.16 for Maricopa and Pima counties, respectively) with observations 13 months prior also supported a 12-month cycle.

Of the four environmental variables we examined, total precipitation was the most variable over time and across counties (Table 4-1). In Maricopa County, the average monthly total precipitation between 1996 and 2017 was 1.49 cm (standard deviation: 1.77 cm, range: 0–9.67 cm). Total precipitation has complex seasonality with peaks in late summer (mean: 2.57–2.70 cm) and late winter or early spring i.e., January through March (mean: 2.05–2.39 cm), and a three-month nadir before the late summer peak (mean: 0.28–0.47 cm). Late winter precipitation was the most variable across study period. Annual total precipitation was highest in 2004 (26.51 cm) and lowest in 2012 (13.67 cm), with no indication of a long-term increase or decrease during the study period. In Pima County, the average monthly total precipitation between 1996 and 2017 was 2.27 cm (standard deviation: 2.82 cm, range: 0–16.64 cm). Monthly total precipitation

typically peaked in July (mean: 6.68 cm) with a preceding two- to three-month nadir (mean: 0.23–1.26 cm). As in Maricopa County, there was no consistent long-term trend in annual total precipitation, but it was less variable in Pima County. Years of increased and decreased precipitation coincided with Maricopa County for some years (e.g., 2006, 2008, 2009).

Average PM_{10} concentrations were higher in Maricopa County (34.05 $\mu g/cm^3$) than Pima County (28.96 $\mu g/cm^3$). PM_{10} concentration in Maricopa County declined over the study period, but was stable in Pima County. In addition to these long-term trends, there was considerable variability in average monthly PM_{10} concentration by year and evidence of seasonality. In both counties, PM_{10} concentrations were bimodal with peaks in May or June and November. Average temperature (degrees Celsius) was higher in Maricopa County than Pima County (21.2° vs. 20.2°). In both counties, there was an increase in average annual temperature during the last three years of the study period. Average wind speed (m/s) was similar across both counties (1.71 m/s and 1.82 m/s in Maricopa and Pima counties, respectively). Average wind speed gradually increased from a nadir in December to a peak in June. In Maricopa County, average wind vector direction gradually changed from south-easterly (149.30°) in January to south-westerly (209.00°) in June. In Pima County, average wind vector direction gradually changed from south-westerly (205.15°) in January to southerly (180.26°) in August.

We examined concurrent and up to 24-month lagged relationships between environmental factors (total precipitation, average temperature, average wind speed, and average PM_{10}) and adjusted and unadjusted monthly and adjusted seasonal coccidioidomycosis incidence rate. We limit our results to the adjusted monthly and seasonal series because correlations with unadjusted incidence and incidence among persons aged 65 years and older were largely similar

(Figures 4-S3a–4b). Since bivariate relationships were similar, we did not pursue multivariable modeling for these series.

As precipitation varied most between years, it was more likely than other factors to have caused interannual variation in coccidioidomycosis epidemics. In Maricopa County, the correlation heat map displayed negative correlations between monthly incidence rate and same year January–February, previous year March, September–November, and May–June, and 1.5- to two-year lagged July–September precipitation. There were positive correlations between incidence and preceding December, one- to two-year lagged December–January precipitation (Figure 4-1a). In the cross-correlation analysis, monthly incidence rate was negatively correlated with total precipitation lagged one to eight months with two successive increases and decreases in the strength of the correlation (peaks: -0.26 and -0.20) (Figure 4-S1). This was followed by two successive increases and decreases of positive correlations between 14- and 18-month lagged precipitation and incidence after which correlations were again negative at 19 months. Comparing seasonally-adjusted trends in precipitation and incidence, periods of elevated precipitation appear to be followed by increases in incidence when there are concurrent declines in precipitation (Figure 4-2). In the seasonal analysis, seasonal average incidence rates were positively correlated (range: 0.19, 0.47) with average winter precipitation three to six seasons (i.e., 9–18 months) prior. Concurrent and/or one- to two-season lagged precipitation was negatively correlated (range: -0.18, -0.56) with subsequent seasonal incidence (Figure 4-S2).

In Pima County, there were negative correlations between previous year March, May, and December–January total precipitation and incidence in the heat map analysis. We observed positive relationships between 1.5 to two-year September, previous year October, June, and February–March total precipitation and incidence (Figure 4-1b). In the cross-correlation analysis,

a sinusoidal pattern of alternating positive and negative correlations was observed. The strongest negative correlation was at two months prior (-0.25), while the strongest positive correlation was at eleven months prior (0.18) (Figure 4-S1). Comparing long-term trends in precipitation and incidence, we again observe that periods of elevated precipitation followed by coinciding declines appear to be followed by increases in incidence (Figure 4-2). In the seasonal analysis, preceding winter precipitation was positively correlated with subsequent fall (0.40) and winter (0.19) incidence. There were negative correlations (range: -0.15, -0.46) between concurrent and one- to three-season lagged precipitation and seasonal average incidence rate (Figure 4-S2).

In heat map analysis of average temperature and monthly incidence in Maricopa County, previous year March to May (range: -0.17, -0.46) and preceding January (range: -0.13, -0.38) average temperature was inversely associated with incidence, and preceding July–August and 1.5 to two-year lagged July average temperature were positively associated (range: 0.22, 0.63) with incidence (Figure 4-1a). In the seasonal analysis, preceding and/or previous year winter temperature was inversely associated with incidence and summer temperatures were positively associated with incidence (Figure 4-S2). We did not observe consistent patterns in the comparison between long-term trends in average monthly temperature and incidence (Figure 4-2). In Pima County, one- to six-month lagged and preceding June–July average temperatures were positively associated with incidence, and few correlations were negative (Figure 4-1b). There was no evident temporal trend in average temperature (Figure 4-2). In the seasonal analysis, correlations were again largely positive, although previous year winter and fall temperatures were inversely associated with incidence (Figure 4-S2).

In heat map analysis of average wind speed and incidence in Maricopa County, previous year May to August and December through February average wind speed were negatively

correlated with incidence. Previous year March to April, April to May, and 1.5- to two-year lagged September to November were positively associated with incidence (Figure 41a). In the seasonal analysis, spring and summer incidence were inversely associated with the previous summer wind speed (range: -0.57, -0.43) and incidence in all seasons was associated with previous year's summer wind speed (i.e., 5 to 7 seasons prior). Positive correlations were observed with winter incidence and previous year's fall wind speed and spring wind speed and spring and summer incidence (Figure 4-S2). Increases and decreases in average wind speed coincided with same-direction changes in incidence between 2003 and 2016 (Figure 4-2). In Pima County, previous year February was negatively correlated with incidence (Figure 4-1b). In the seasonal analysis, there were negative correlations between lagged wind speed and incidence for most months and lags (Figure 4-S2). The strongest negative correlations were for the previous year's winter. There was no meaningful change in average wind speed in Pima County (Figure 4-2).

Associations with PM_{10} and incidence also varied by county. In Maricopa County, one- to two-year lagged June through October and previous year April to May PM_{10} were negatively associated with incidence (range: -0.11, -0.64) in the heat map analysis (Figure 4-1a). There were positive correlations (range: 0.20, 0.30) between preceding February through March PM_{10} and incidence. In the seasonal analysis, there were negative correlations between two- to eight-season lagged PM_{10} and incidence (Figure 4-S2). In the trend analysis, there was some support for a relationship between concurrent PM_{10} and incidence. In Pima County, correlations with PM_{10} were mostly zero or weakly positive in the heat map analysis with the exception of negative correlations between incidence and one- to two-year lagged May through September and

previous year December through February PM_{10} (Figure 4-1b). Trends in PM_{10} grossly followed incidence rate trends (Figure 4-2).

Based on these results, we created nineteen (seven total precipitation; four average temperature; five average wind speed; three average PM_{10}) and twelve (seven total precipitation; two average temperature; one average wind speed; two average PM_{10}) additional weather-related variables for Maricopa and Pima counties, respectively, summarizing the observed relationships. Pearson correlation coefficients for these composite variables and monthly incidence rates are listed in Table 4-2. We selected the following predictors for inclusion in multivariable linear regression models of log monthly incidence rate based on the strongest positive and negative correlations for each environmental variable: one- to two-year lagged December–January and 1.5- to two-year lagged July–September average total precipitation; preceding January and 1.5 to two-year lagged July average temperature; previous year May to August average wind speed; and one- to two-year lagged June through October PM_{10} for Maricopa County and previous year March and previous year December–January average total precipitation; preceding June–July average temperature; previous year February average wind speed; and one- to two-year lagged May through September PM_{10} for Pima County. The PM_{10} variable was eliminated from the model for Maricopa County because it was highly correlated with one- to two-year lagged December–January total precipitation. Figure 4-3 displays predicted versus observed values of monthly incidence rates between 2003 and 2017 for Maricopa and Pima counties by model. For Maricopa County, the performance of the linear regression model was as follows: root mean square error 3.4; mean absolute error 2.5; and mean absolute percentage error 37.0% Performance was better in Pima County: root mean square error 2.8; mean absolute error 2.2; and mean absolute percentage error 36.1%.

Discussion

We used a variety of methods to identify relationships between environmental factors and coccidioidomycosis incidence in Arizona. We included 20 years of incidence data from Maricopa and Pima counties, which report among the highest numbers of confirmed coccidioidomycosis cases in the U.S. As in previous studies[120], we found evidence of an annual seasonal cycle for incidence with differences in seasonality across counties. We used season-trend decomposition to identify seasonally-adjusted long-term trends in climate and PM_{10} and found approximate concordance, or evidence of a more complex relationship, between incidence and total precipitation, average wind speed, and PM_{10}. Consistent with previous work[8,65,117,119,123], we observed positive correlations between one- to two-year lagged winter precipitation and subsequent monthly incidence rate. Previous studies have reported a suppressive effect of antecedent or concurrent (i.e., fall or winter) precipitation on incidnece.[65,120,121,123] We found negative correlations between previous year September to November and 1.5- to two-year lagged July-September precipitation.

We also found positive correlations between 1.5- to two-year and preceding late summer average temperature and incidence in both counties. Findings in the literature are more mixed, with some studies reporting positive correlations with 3- to 4-month lagged average temperature and incidence[65,122] while others found no correlation[120] or negative correlations between summer temperature and incidence anomalies.[117] In contrast to previous studies reporting no relationships[65,117,120], we found weak negative and positive correlation between precious year (e.g., April to May) average wind speed and incidence in Maricopa County and a stronger negative correlation between previous year February average wind speed and incidence in Pima County. Finally, we found mostly negative correlations between spring and summer to fall PM_{10}

and incidence. This was also reported by Tong et al., and may reflect the anthropogenic components of PM_{10} as opposed to soil borne dust.[121] Previous studies have found positive correlations between dust storms or PM_{10} and incidence.[65,119,122]

We also constructed multivariable models of coccidioidomycosis incidence and weather in both counties. We constructed composite variables to summarize weather-incidence relationships and evaluated model prediction of monthly incidence rate. Model performance was suboptimal, particularly after 2011. Few studies have attempted to predict coccidioidomycosis incidence. Previous analyses by Zender and Talamantes used linear and autoregressive moving average regression models to predict incidence in Kern County, California and found that models including lagged incidence could more accurately predict incidence than models including weather-related variables. The addition of environmental variables had minimal effect on model accuracy.[148–150]

We attempted to address several methodological concerns in the weather and coccidioidomycosis literature. Contrary to our hypothesis, we found that adjusting for surveillance changes did not meaningfully affect relationships between incidence and weather. Surveillance changes only applied to nine of 20 years of incidence data, and the potential bias introduced by them may not be substantially time-varying. Similarly, restricting the incidence time series to cases aged 65 years and older did not alter conclusions from bivariate analyses. We hypothesized that cases in this age group might be more similar with respect to time between exposure and case report. Although age is associated with comorbidities and comorbidities are determinants of disease severity[71], disease presentation and careseeking among older adults might be more variable than we had assumed.

We also sought to understand the influence of methodological choices on weather-incidence analysis. We compared season- and month-level aggregation of incidence and weather data and found that seasonal analyses were largely concordant with monthly analysis. Weather-related predictors are highly correlated, making variable selection and model development a challenge. Finally, while we attempted to simulate prospective evaluation of model performance, we used data on confirmed cases that had been processed to remove duplicates and cases without positive laboratory test results from high specificity tests (e.g., immunodiffusion, culture). Although case reports are routinely processed and cleaned, model performance might be worse using data collected in real-time.

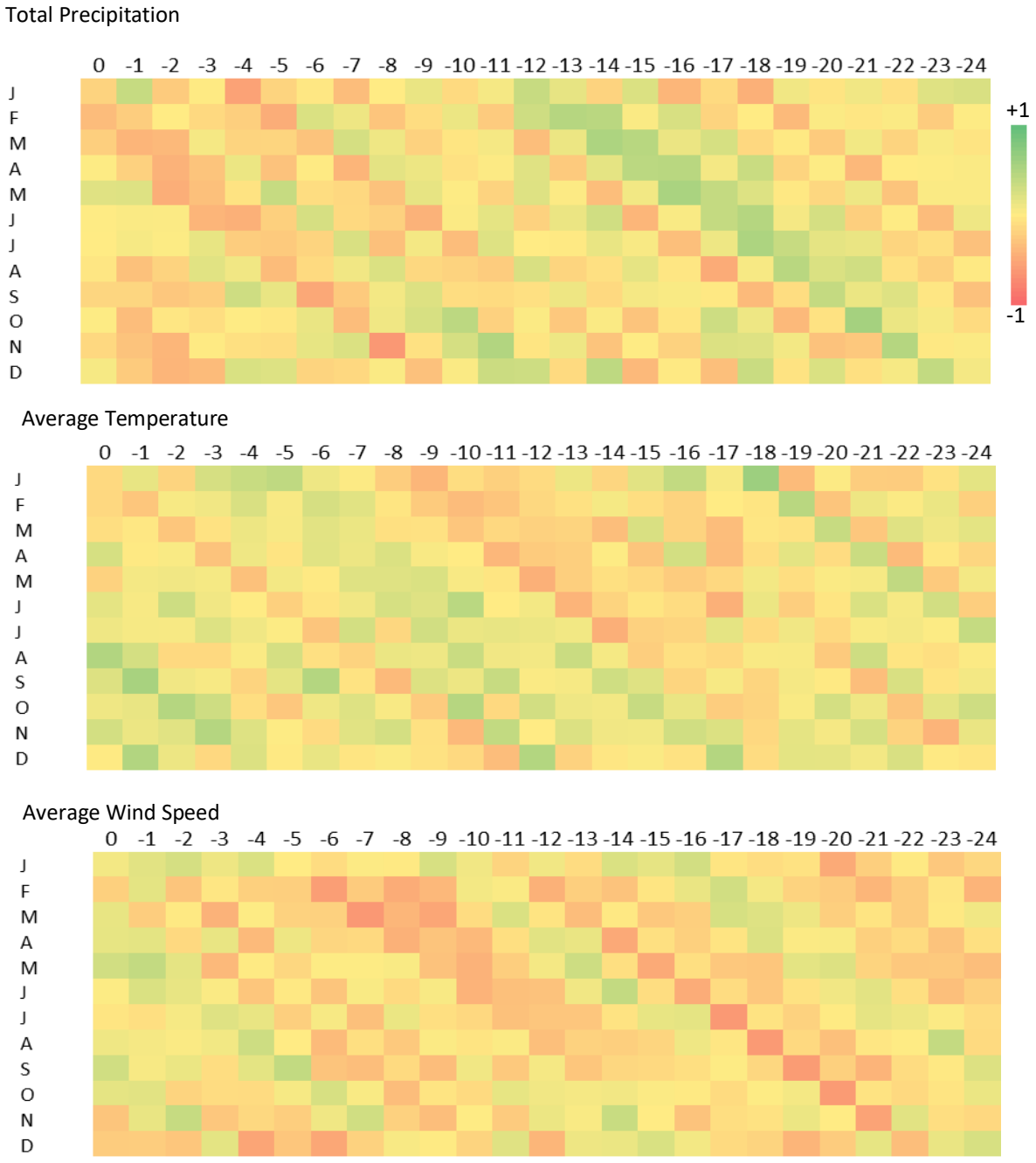
As previous authors have observed, case reports are a coarse measure of fungal activity and risk of infection. In addition to the approximately 40% of infections that are asymptomatic, an unknown proportion are not detected or even medically attended. Coccidioidomycosis also has a relatively long incubation period of one to three weeks.[28] Enhanced surveillance of reported cases in Arizona found that time between symptom onset and report was also lengthy and varied substantially across patients.[75] Previous studies have adjusted for time to report by subtracting a single value from case report dates, which does not account for heterogeneity, and sensitivity analyses suggest that single-value adjustment does not substantially affect estimated associations between climate and incidence.[133]

Several features of the study period might have also contributed to difficulty in accurate forecasting. Despite our adjustment for surveillance changes, reported case counts exhibited differing temporal dynamics after 2009 as compared with earlier years. While these years coincide with changes in laboratory testing and reporting, it is likely that other factors also contributed to these differences. These phenomena might be related to careseeking and testing,

in-migration of susceptible persons, and/or unknown environmental factors, none of which were included in our models. It is also possible that our environmental measures were not measured at the appropriate spatial scales. The distribution of *Coccidioides* in soil appears to be highly focal and irregular[2,151], and a recent air sampling study found unexplained spatiotemporal heterogeneity.[22] Thus, total precipitation, for example, across an entire county does not capture variability in sub-meter scale soil moisture, temperature, and small mammal behavior. Similarly, we used PM_{10} as a crude proxy for arthroconidia density, though it includes particulates from a variety of natural and anthropogenic sources.[131] Small-scale field studies of *Coccidioides* in the soil and air would facilitate our understanding of these dynamics and development of better measures of relevant environmental drivers of fungal activity.

While weather likely influences *Coccidioides* distribution and growth, the inherent stochasticity of natural systems, including climate and *Coccidioides* ecology, might limit our ability to predict incidence at useful time horizons and with acceptable accuracy. Forecasting models might be strengthened by incorporating measures of careseeking and testing from local healthcare providers and reference laboratories. At the time of this analysis, long-term time series of these variables were unavailable. Direct measurement of airborne arthroconidia would allow for inferences about contemporaneous risk of infection and alert public health authorities and the healthcare system of later increases in the number of patients with coccidioidomycosis. Since there are no measures to prevent infection in endemic areas, this strategy might be as actionable as an accurate prediction model and allow for the collection of long-term data on fungal activity, potentially providing insights into the ecology of *Coccidioides*.

Figure 4-1a. Correlation heat maps for adjusted coccidioidomycosis incidence by calendar month and 0–24-month lagged environmental factors in Maricopa County, 1998 – 2017



Average PM_{10}

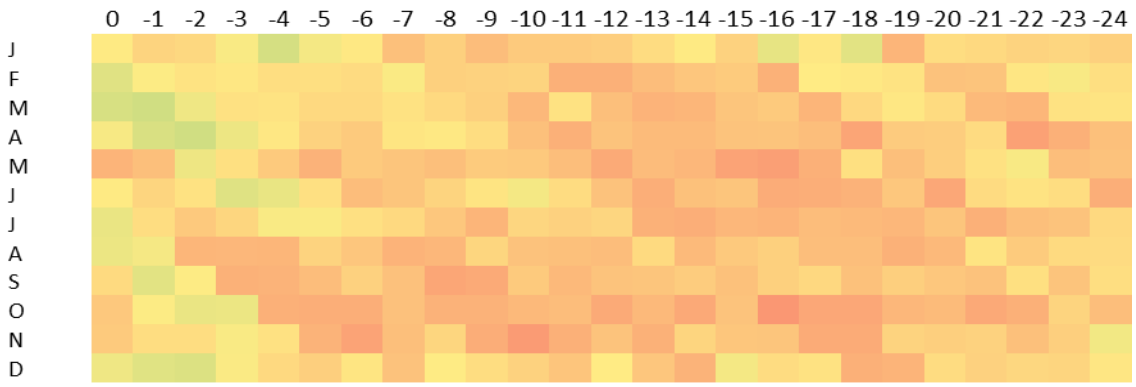
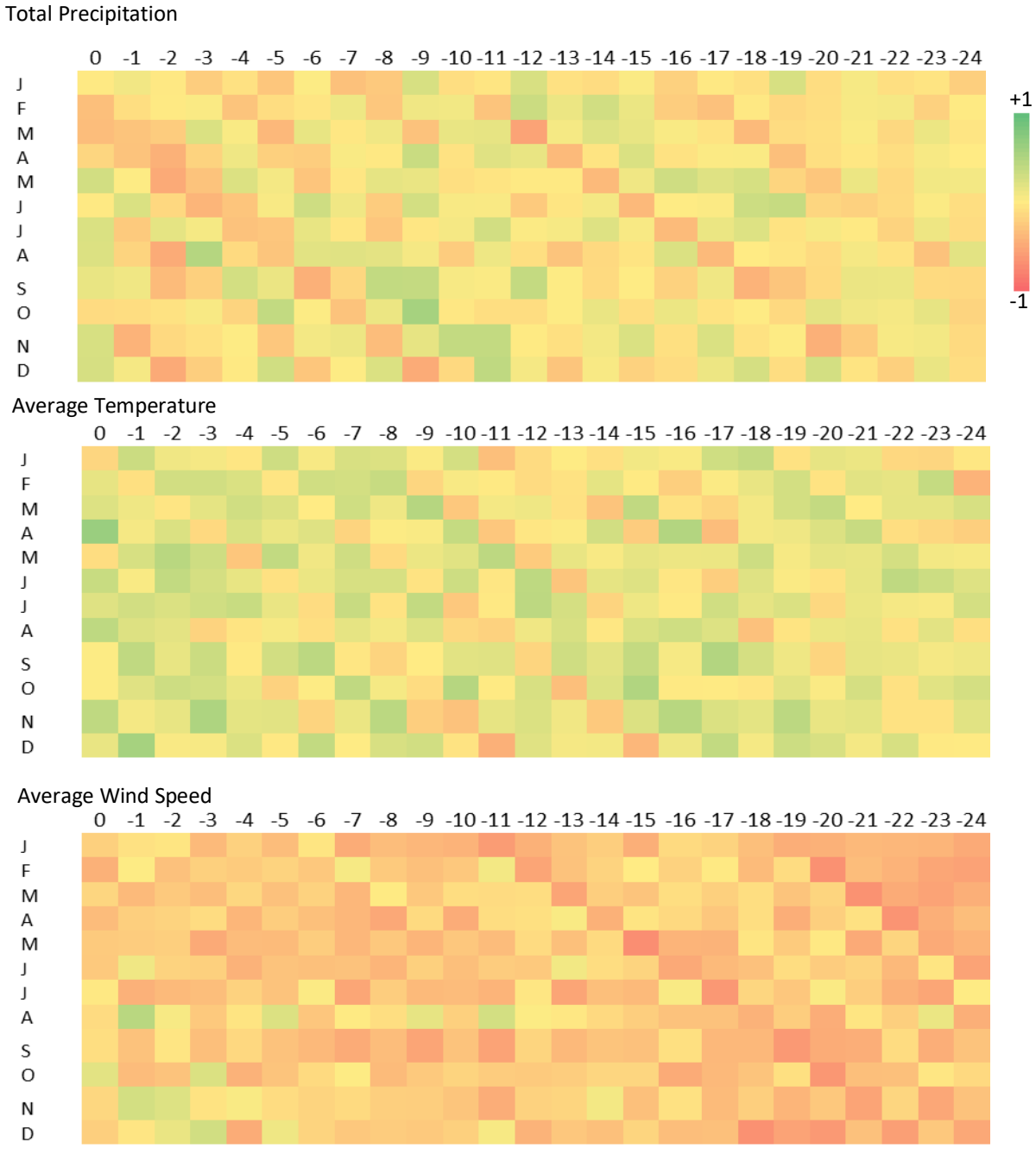
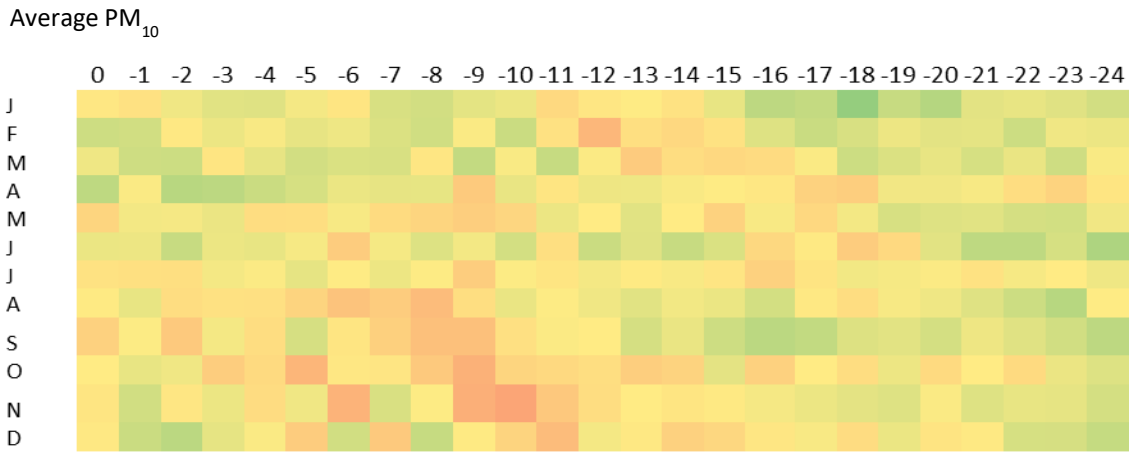


Figure 4-1b. Correlation heat maps for adjusted coccidioidomycosis incidence by calendar month and 0–24-month lagged environmental factors in Pima County, 1998 – 2017




Average PM10
0 -1 -2 -3 -4 -5 -6 -7 -8 -9 -10 -11 -12 -13 -14 -15 -16 -17 -18 -19 -20 -21 -22 -23 -24
J
F
M
A
M
J
J
A
S
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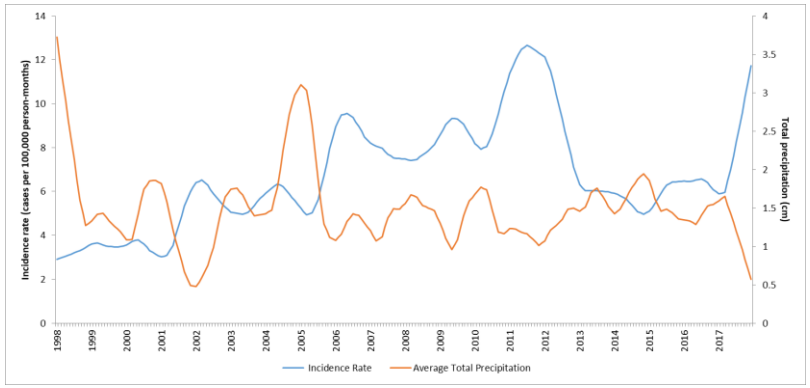
D

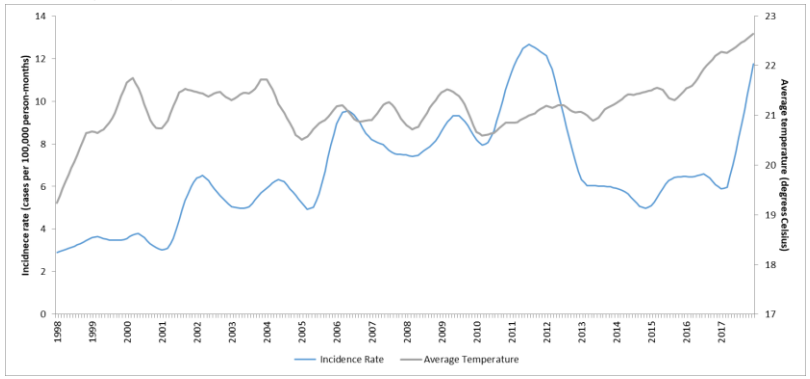
Figure 4-2. Season-trend decomposition for adjusted monthly coccidioidomycosis incidence and environmental factors in Maricopa and Pima counties, 1998 – 2017

Maricopa County

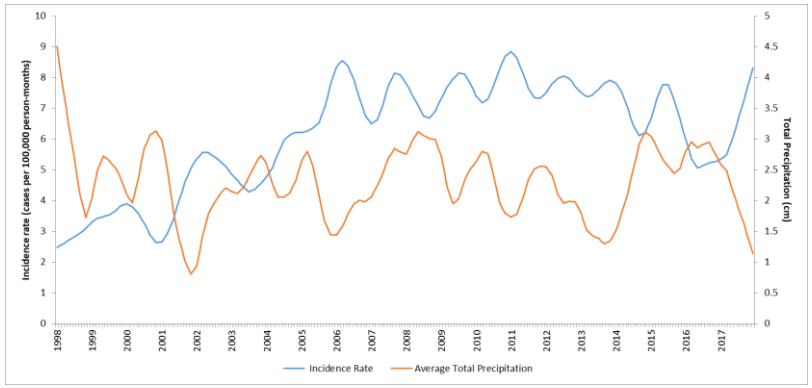
Average Total Precipitation

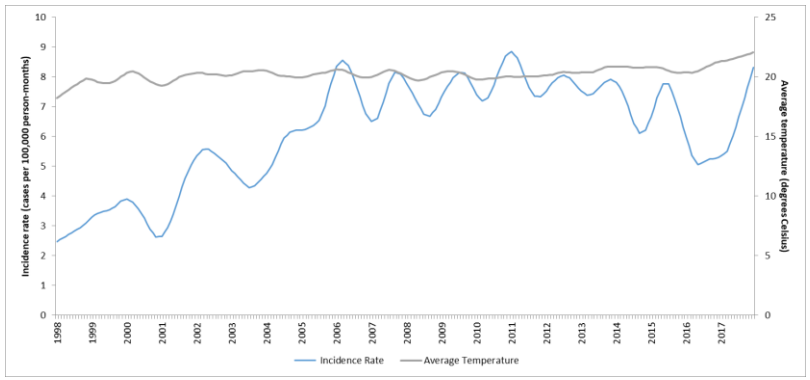


Average Temperature



Pima County

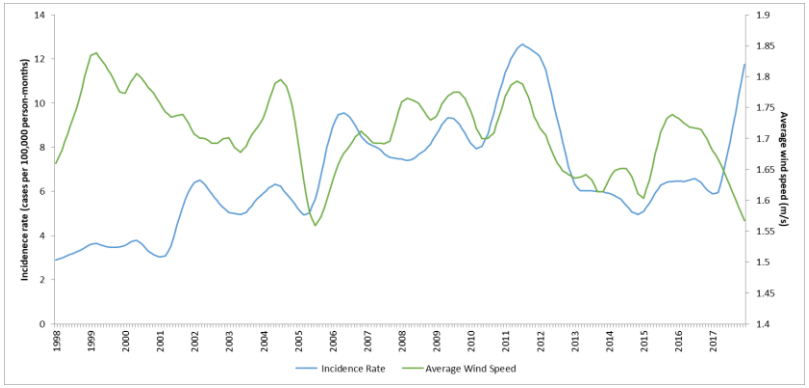


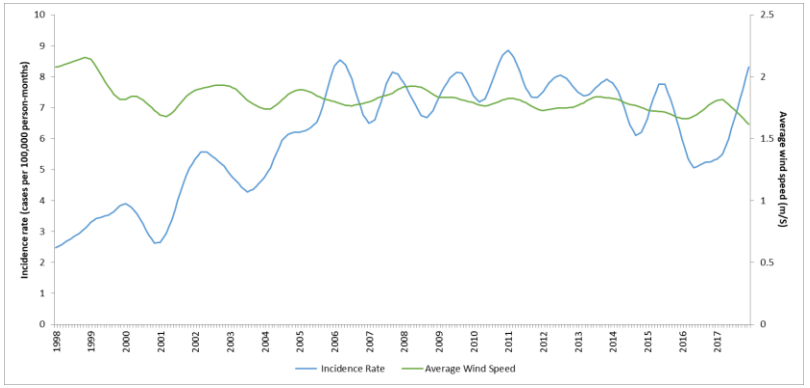


Maricopa County

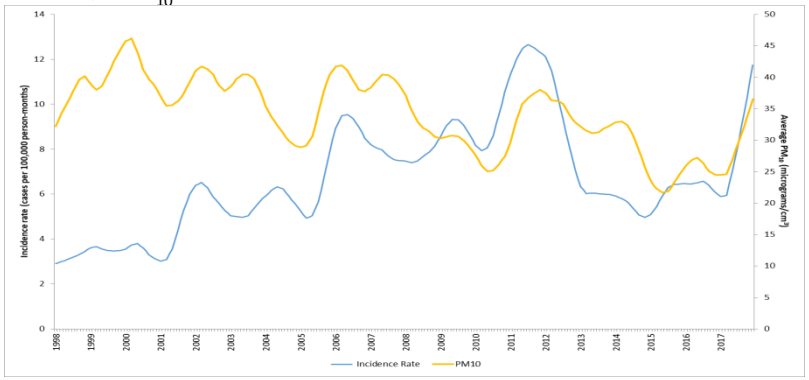
Pima County

Average Wind Speed





Average PM_{10}



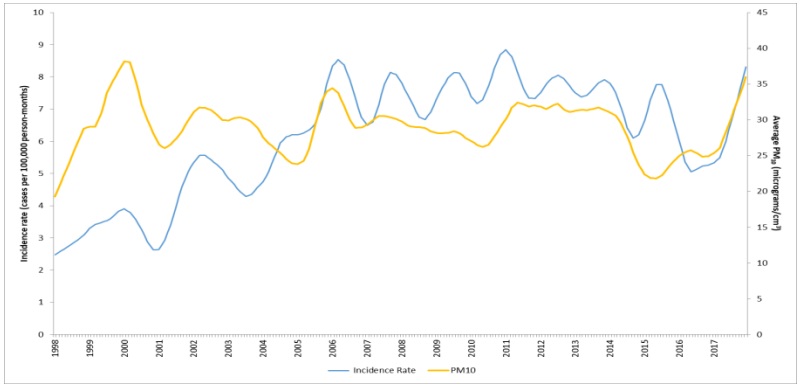


Figure 4-3. Predicted vs. observed adjusted coccidioidomycosis incidence in Maricopa and Pima counties, 2003 – 2017

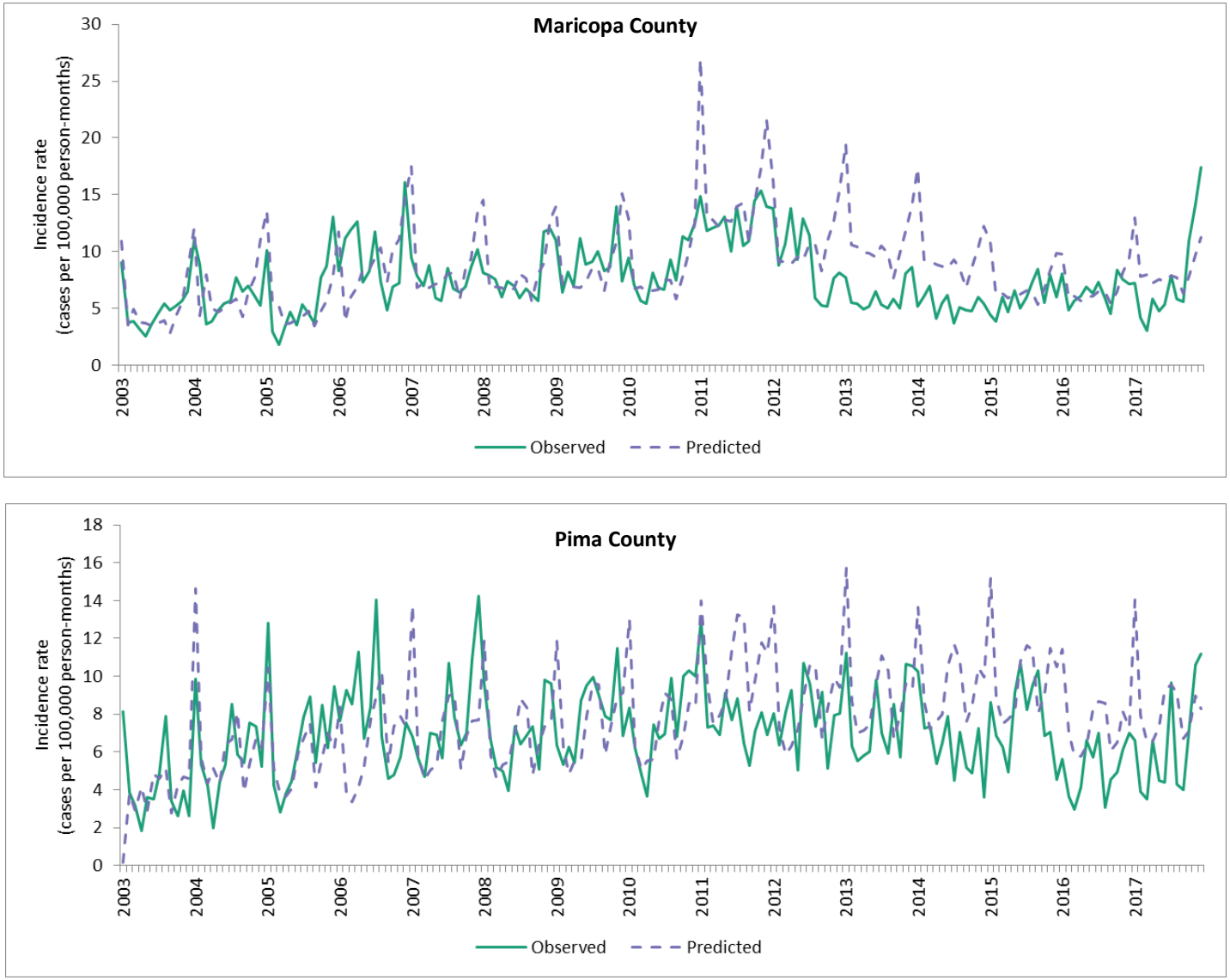
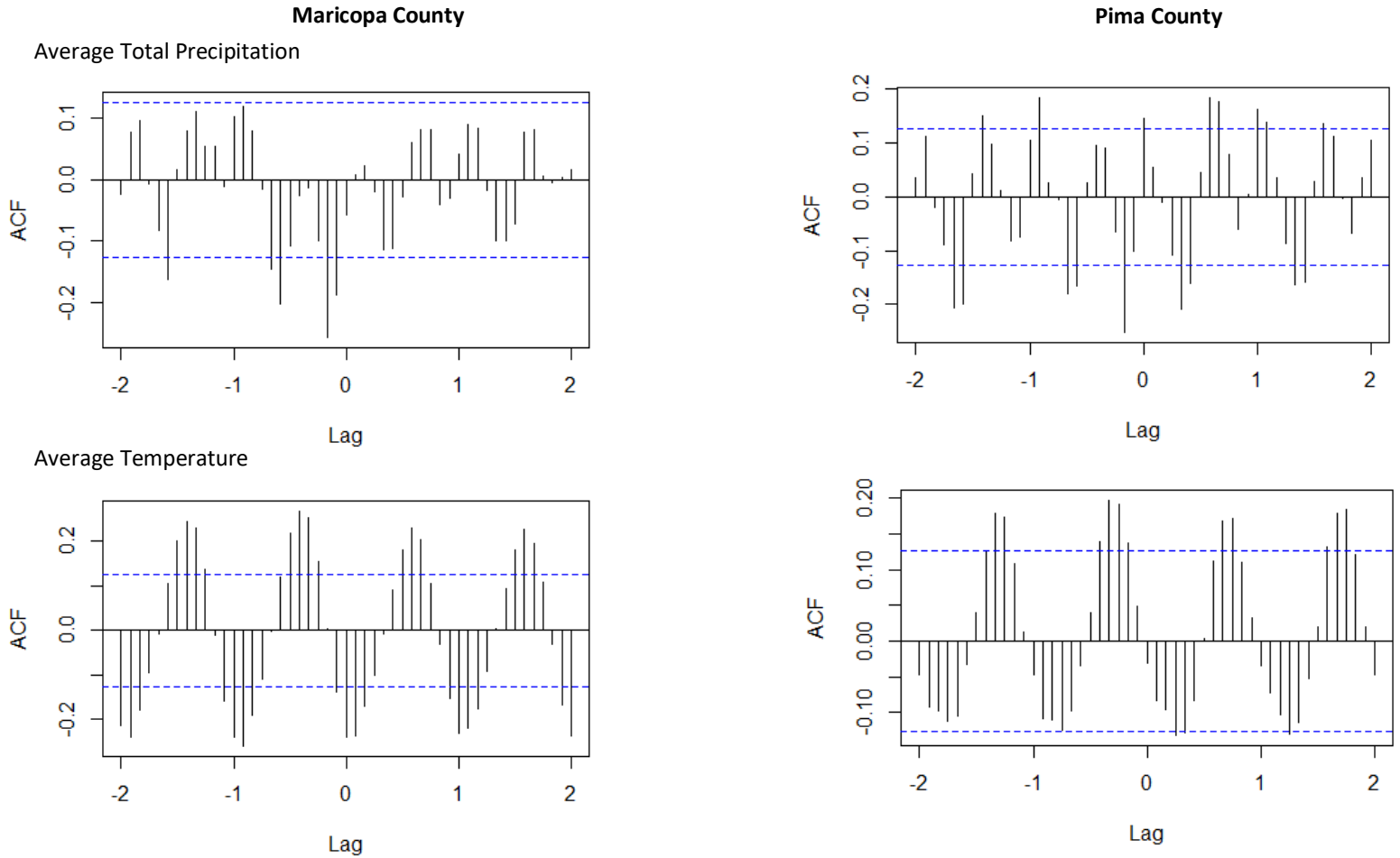
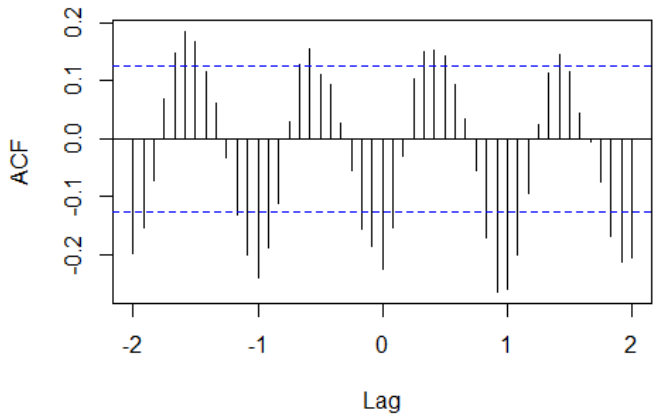


Figure 4-S1. Cross-correlation plots for adjusted coccidioidomycosis incidence and environmental factors in Maricopa and Pima counties, 1998 – 2017

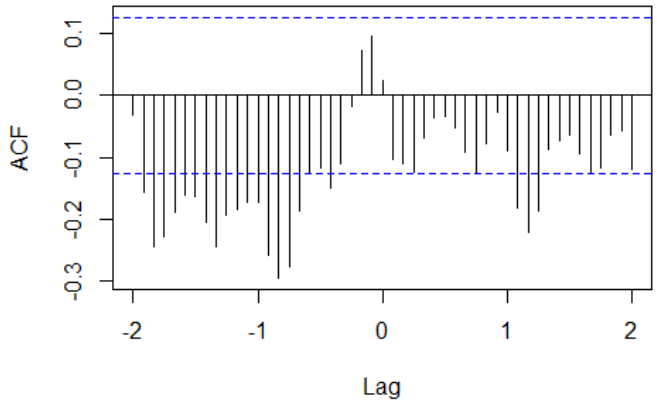


Maricopa County

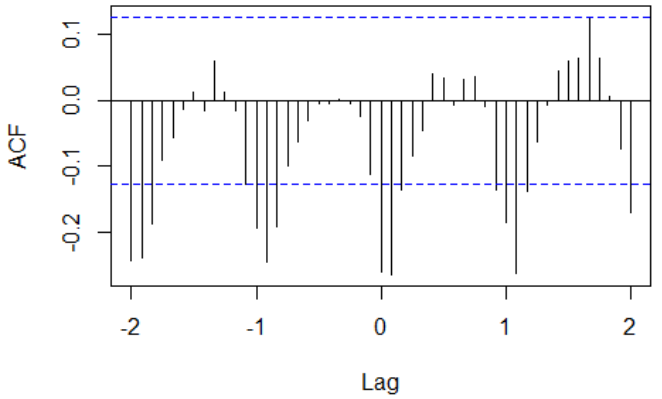
Average Wind Speed



Average PM_{10}



Pima County



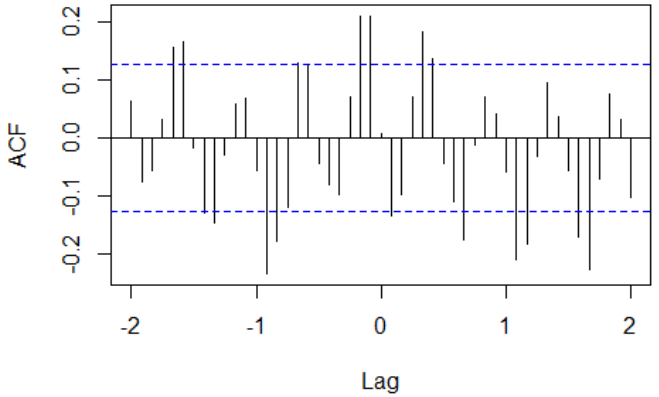
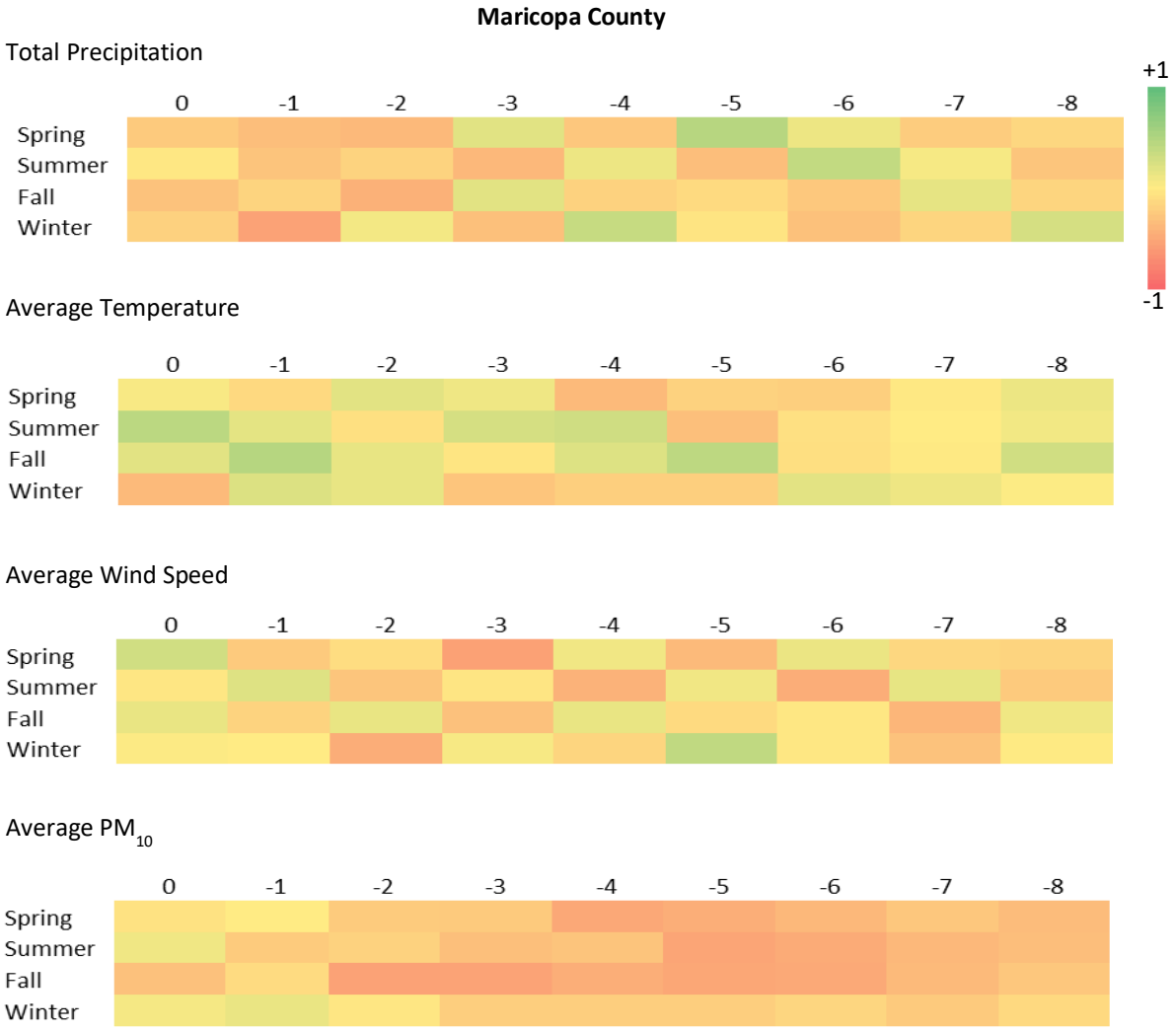


Figure 4-S2. Correlation heat maps for adjusted coccidioidomycosis incidence by meteorological season and 0–8-season lagged environmental factors in Maricopa and Pima counties, 1998 – 2017



Pima County

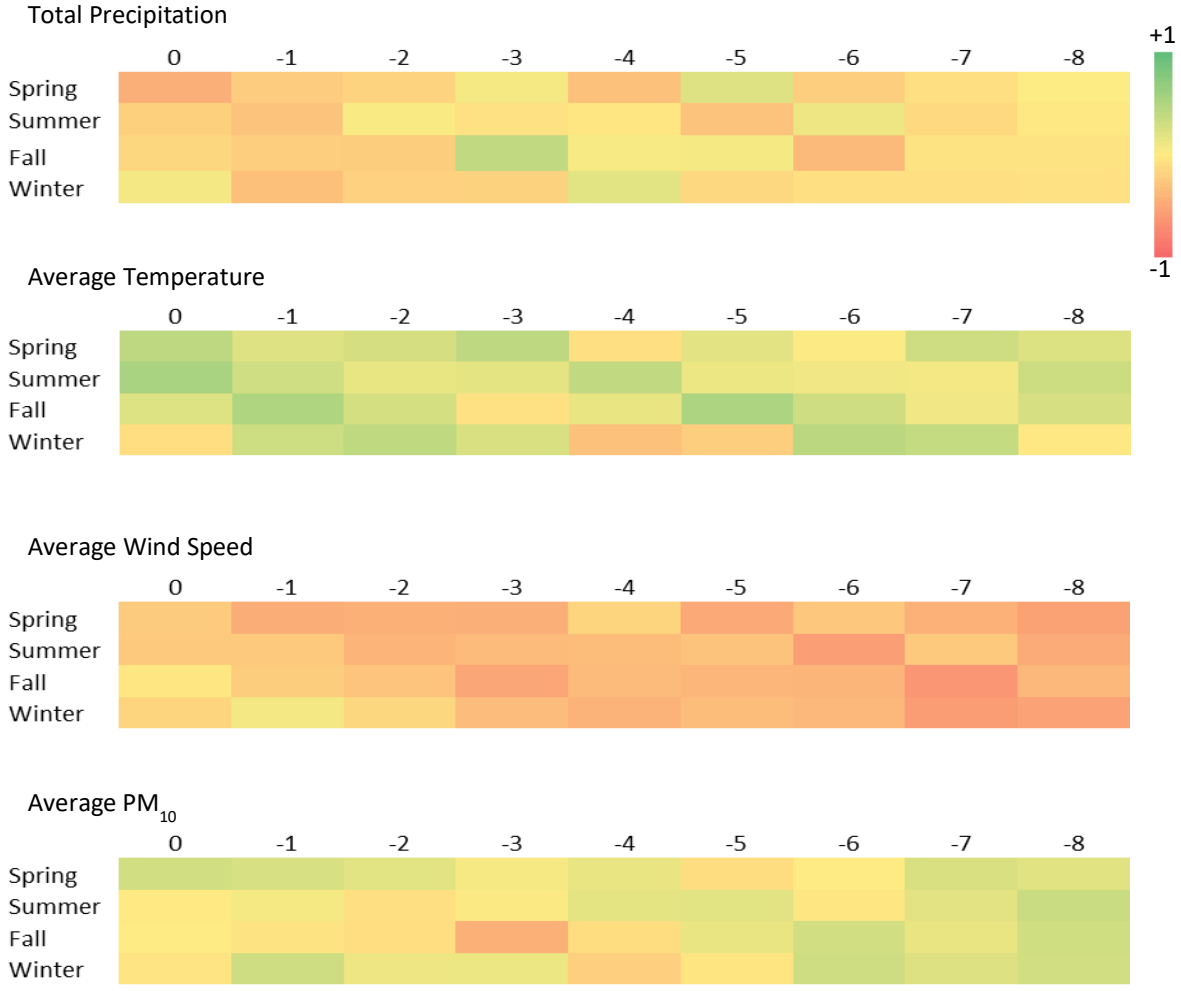
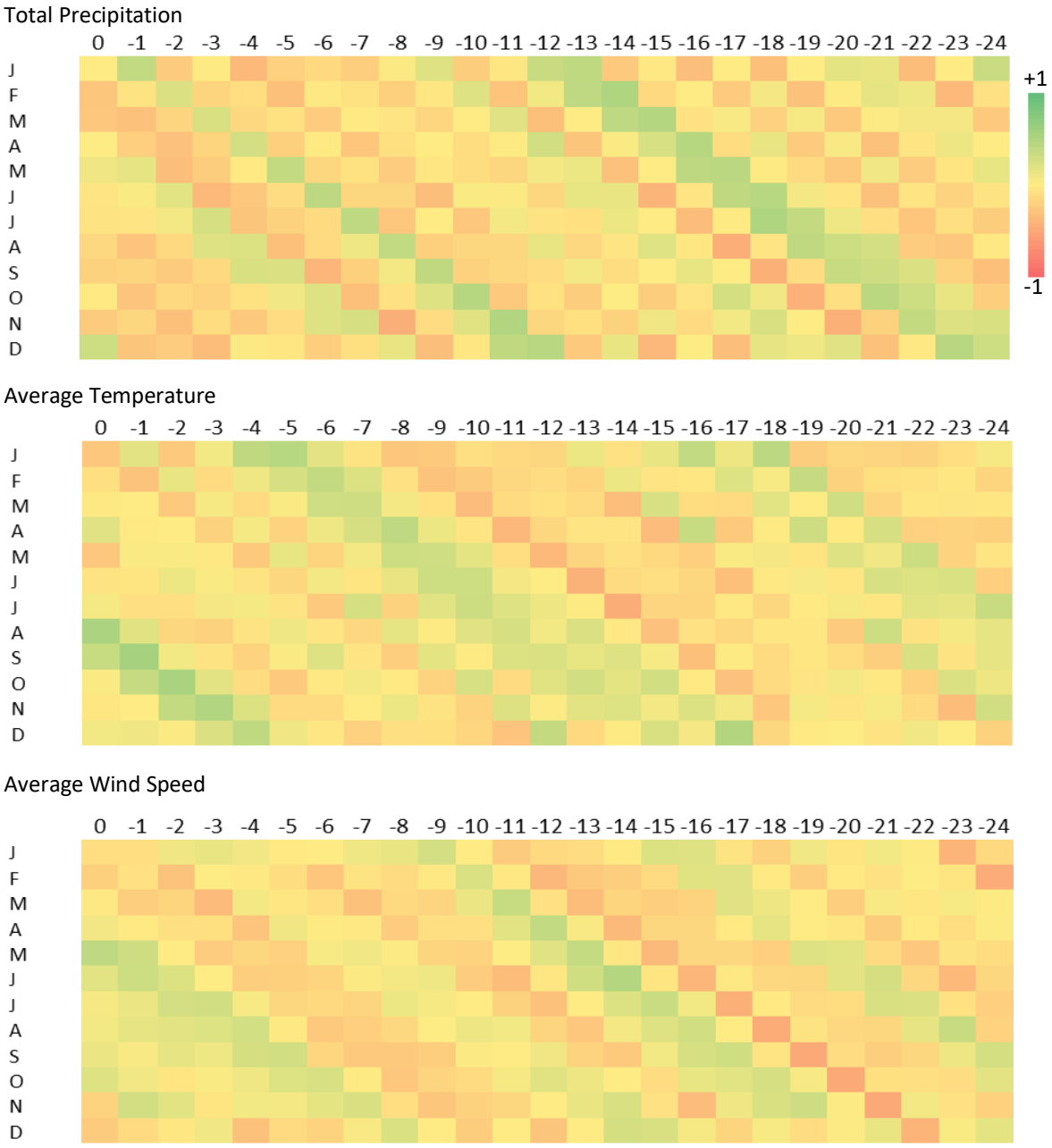
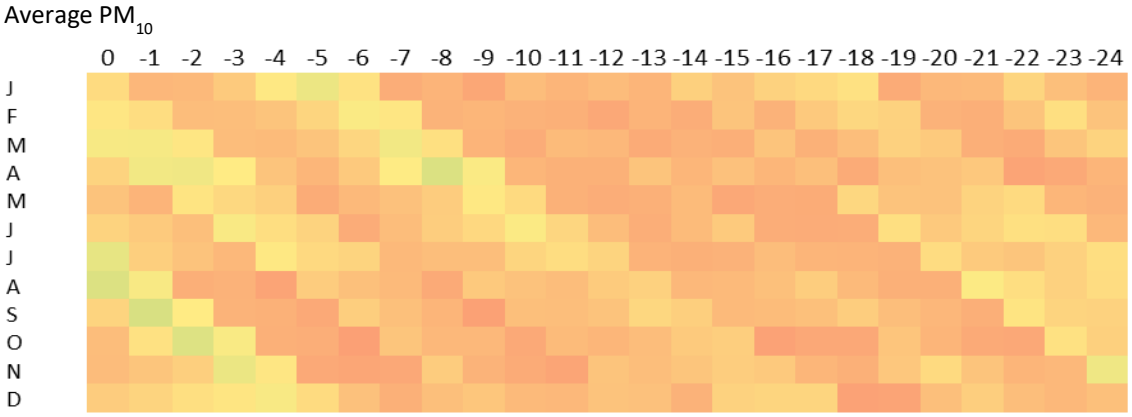

Total Precipitation
0 -1 -2 -3 -4 -5 -6 -7 -8
Spring
Summer
Fall
Winter
+1
-1
Average Temperature
0 -1 -2 -3 -4 -5 -6 -7 -8
Spring
Summer
Fall
Winter
Average Wind Speed
0 -1 -2 -3 -4 -5 -6 -7 -8
Spring
Summer
Fall
Winter
Average PM10
0 -1 -2 -3 -4 -5 -6 -7 -8
Spring
Summer
Fall
Winter

Figure 4-S3a. Correlation heat maps for unadjusted coccidioidomycosis incidence by calendar month and 0–24-month lagged environmental factors in Maricopa County, 1998 – 2017




Average PM10
0 -1 -2 -3 -4 -5 -6 -7 -8 -9 -10 -11 -12 -13 -14 -15 -16 -17 -18 -19 -20 -21 -22 -23 -24
J
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M
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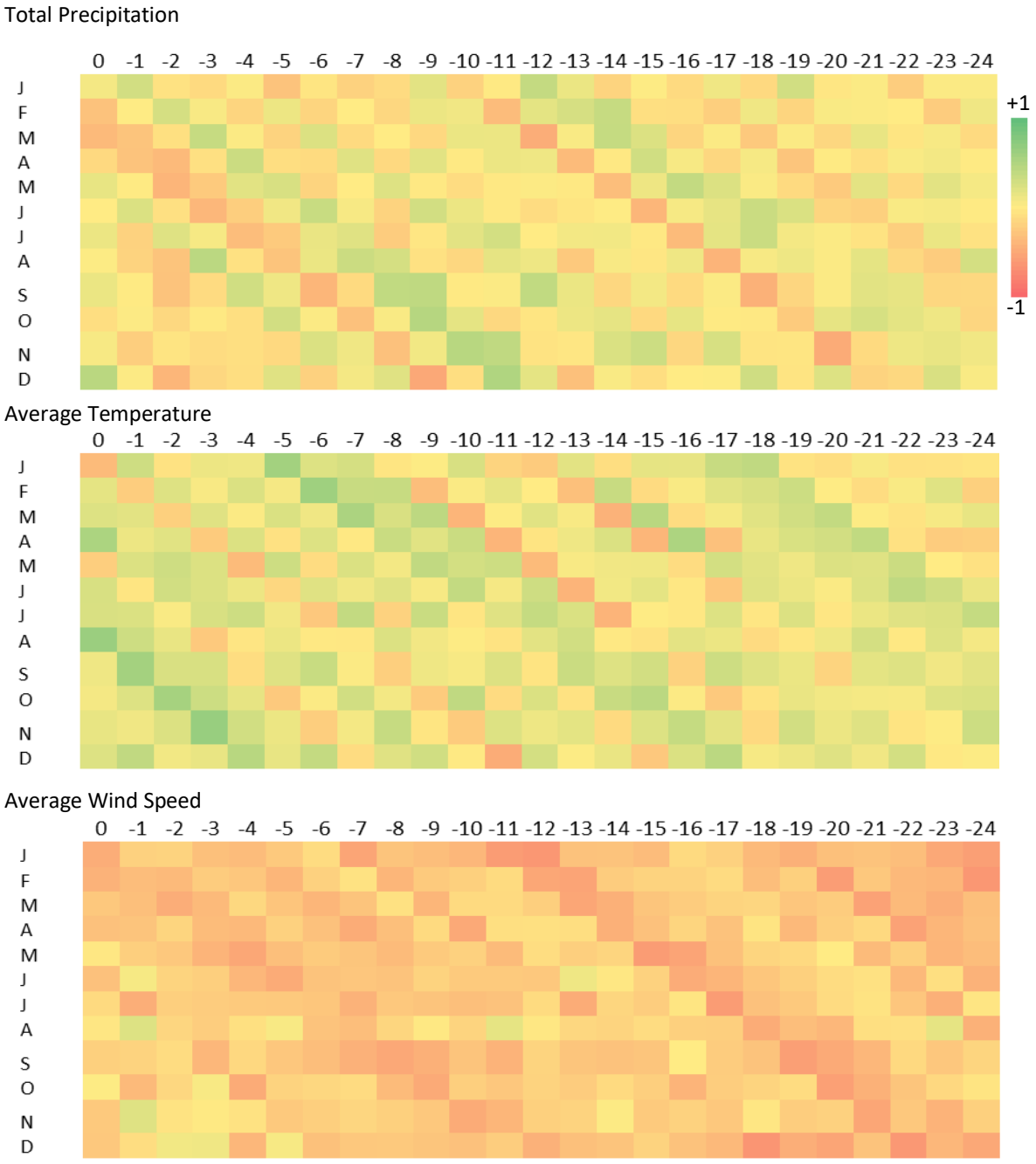
Figure 4-S3b. Correlation heat maps for unadjusted coccidioidomycosis incidence by calendar month and 0–24-month lagged environmental factors in Pima County, 1998 – 2017



Average PM_{10}

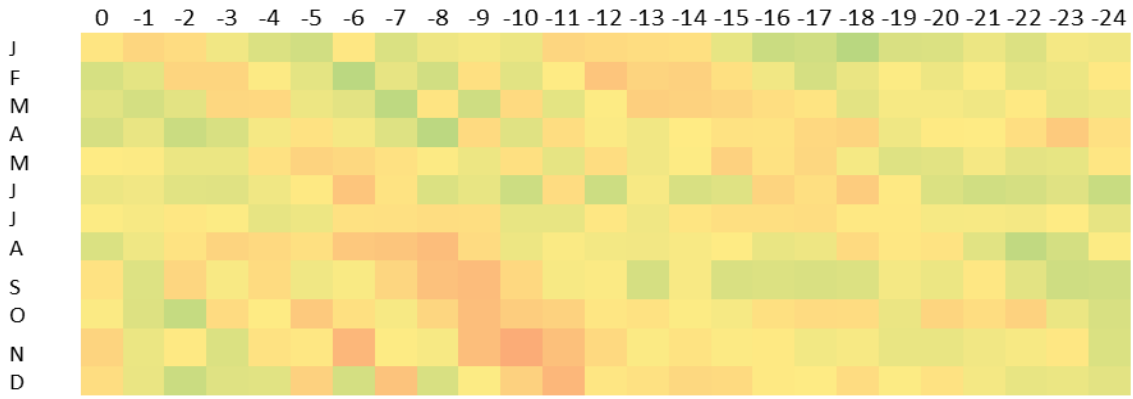
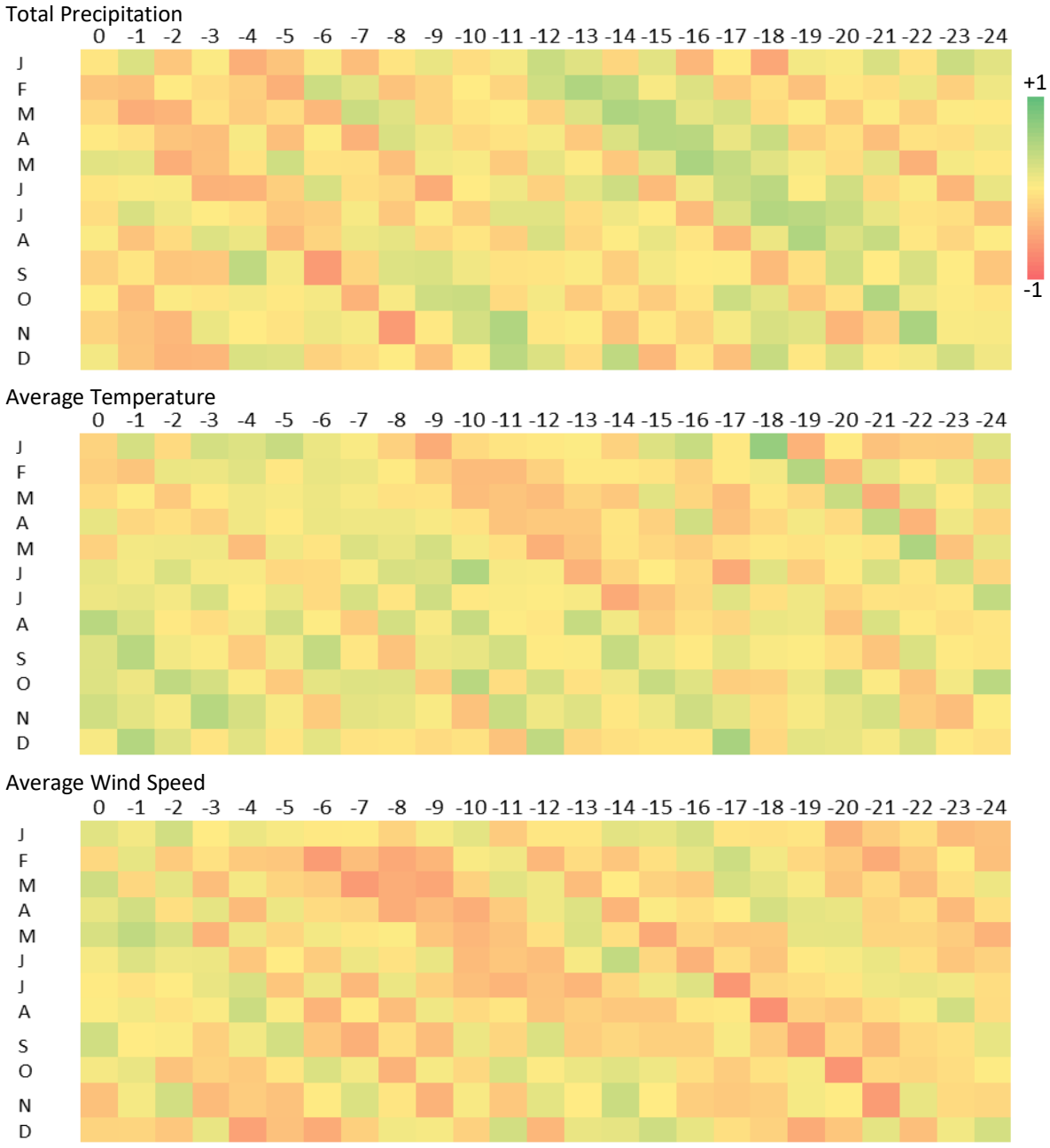
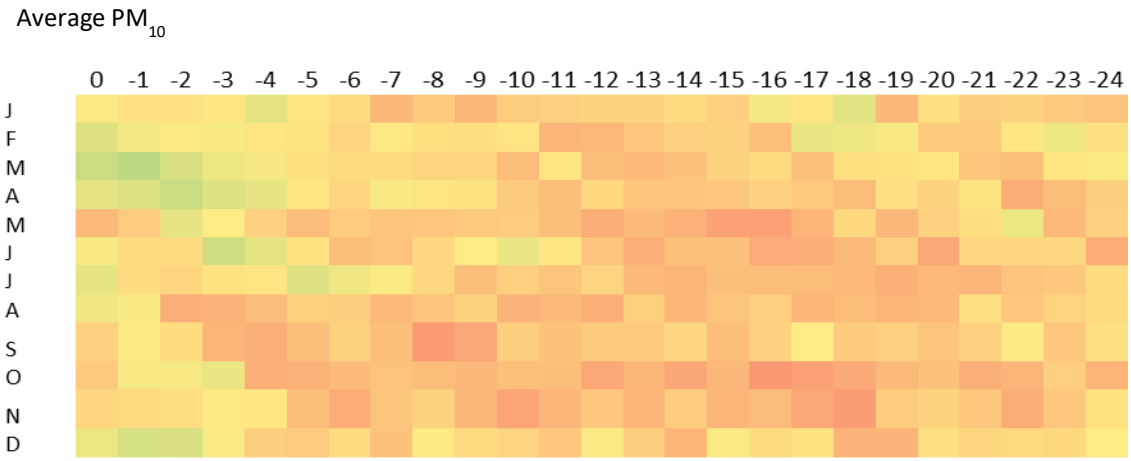


Figure 4-S4a. Correlation heat maps for coccidioidomycosis incidence among persons 65 years and older by calendar month and 0–24-month lagged environmental factors in Maricopa County, 1998 – 2017




Average PM10
0 -1 -2 -3 -4 -5 -6 -7 -8 -9 -10 -11 -12 -13 -14 -15 -16 -17 -18 -19 -20 -21 -22 -23 -24
J
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M
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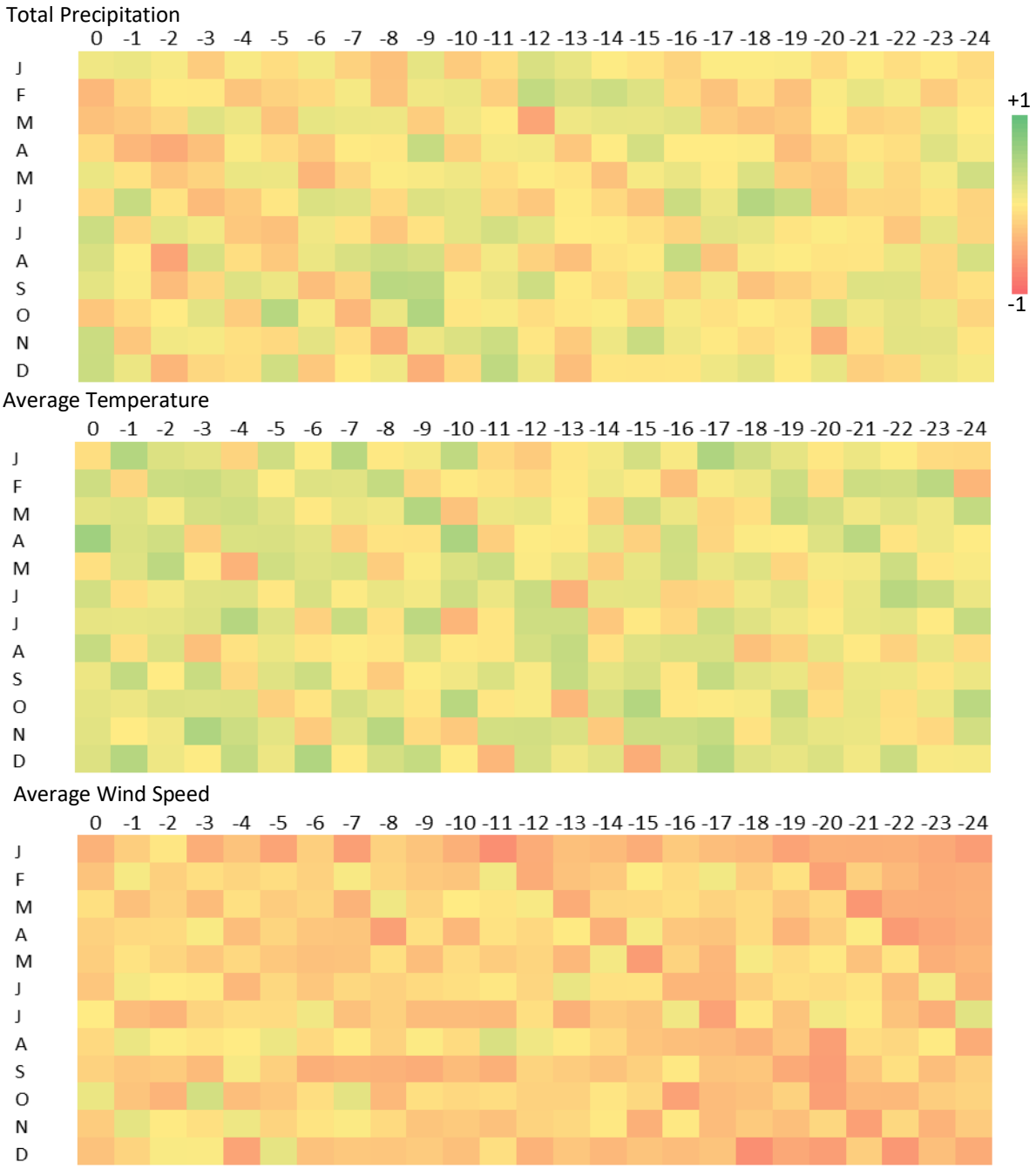
Figure 4-S4b. Correlation heat maps for coccidioidomycosis incidence among persons 65 years and older by calendar month and 0–24-month lagged environmental factors in Pima County, 1998 – 2017



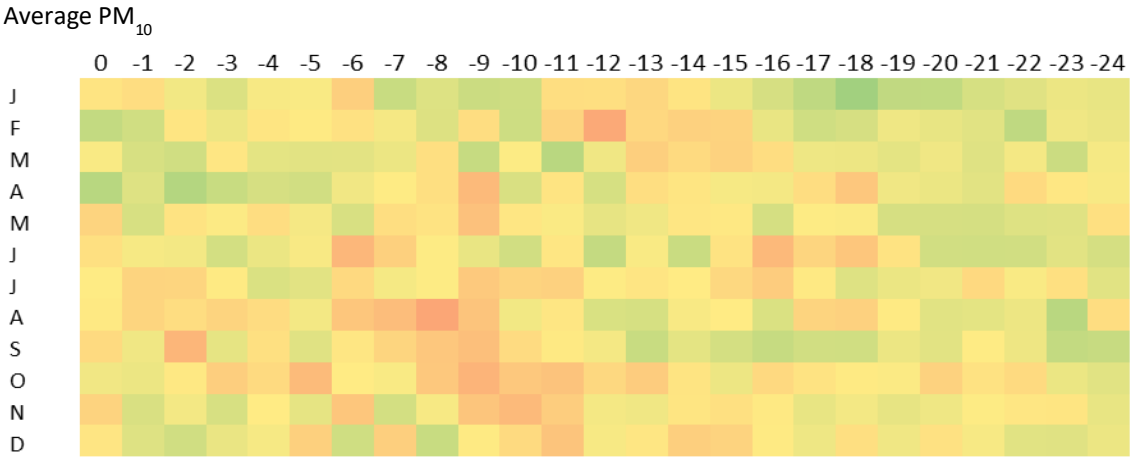

Average PM10
0 -1 -2 -3 -4 -5 -6 -7 -8 -9 -10 -11 -12 -13 -14 -15 -16 -17 -18 -19 -20 -21 -22 -23 -24
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Table 4-1. Description statistics for monthly coccidioidomycosis incidence and environmental factors in Maricopa and Pima counties, 1998 – 2017

	Maricopa		
	Mean (SD)	Median (IQR)	Range
Incidence rate (cases per 100,000 person-months)			
Unadjusted incidence rate	9.84 (7.50)	7.46 (4.88, 11.98)	0.89, 35.59
Bias-adjusted incidence rate	6.69 (3.23)	6.02 (4.50, 8.37)	0.89, 17.39
Bias-adjusted incidence rate - 65+ years only	14.47 (7.55)	13.10 (9.15, 18.33)	1.95, 39.56
Environmental factors			
Average total precipitation (cm)	1.40 (1.77)	0.88 (0.15, 2.29)	0.00, 9.67
Average temperature (ºC)	21.18 (8.05)	20.62 (13.70, 29.24)	8.11, 34.20
Average wind speed (m/s)	1.71 (0.28)	1.73 (1.47, 1.95)	0.98, 2.45
Average PM_{10} (micrograms/m^3)	34.05 (9.80)	32.60 (26.51, 40.23)	16.56, 63.55
	Pima		
	Mean (SD)	Median (IQR)	Range
Incidence rate (cases per 100,000 person-months)			
Unadjusted incidence rate	7.59 (4.05)	6.85 (4.57, 9.99)	0.81, 20.34
Bias-adjusted incidence rate	6.15 (2.66)	6.13 (4.31, 7.85)	0.81, 14.23
Bias-adjusted incidence rate - 65+ years only	11.48 (5.56)	11.40 (7.06, 15.51)	0.85, 27.98
Environmental factors			
Average total precipitation (cm)	2.29 (2.82)	1.19 (0.20, 3.54)	0.00, 16.64
Average temperature (ºC)	20.23 (7.69)	20.16 (13.27, 27.92)	6.51, 31.77
Average wind speed (m/s)	1.82 (0.33)	1.84 (1.58, 2.08)	1.01, 2.76
Average PM_{10} (micrograms/m^3)	28.96 (7.57)	27.58 (23.37, 33.75)	10.51, 57.96

Table 4-2. Correlations between for adjusted monthly coccidioidomycosis incidence and composite environmental variables in Maricopa and Pima counties, 1998 – 2017

Environmental Variable	Pearson Correlation Coefficient
Maricopa County	
Total Precipitation	
one- to two-year lagged December–January	0.46
preceding December	0.24
previous year May–June	0.05
preceding January-February	-0.07
previous year September–November	-0.26
previous year March	-0.27
1.5- to two-year lagged July–September	-0.27
Average Temperature	
1.5 to two-year lagged July	0.28
preceding July–August	0.24
previous year March–May	-0.20
preceding January	-0.26
Average Wind Speed	
1.5- to two-year lagged September–November	0.14
previous year April–May	0.10
previous year March–April	0.10
preceding December-February	-0.22
previous year May–August	-0.26
Average PM10	
preceding February–March	-0.17
previous year April–May	-0.33
one- to two-year lagged June–October	-0.40
Pima County	
Total Precipitation	
previous year March	-0.29
1.5 to two-year September	-0.15
previous year October	-0.12
previous year June	-0.22
previous year February–March	-0.18
previous year May	0.12
previous year December–January	0.20
Average Temperature	
preceding June–July	0.35
one- to six-month lagged	0.18
Average Wind Speed	
previous year February	-0.51

Average PM10	
previous year December–February	-0.09
one- to two-year lagged May–September	0.23

CHAPTER 5: LAND DEVELOPMENT AND REPORTED COCCIDIOIDOMYCOSIS INCIDENCE IN CENTRAL AND SOUTHERN ARIZONA

Background

Coccidioidomycosis is an infectious disease caused by inhalation of spores produced by *Coccidioides* spp., fungi endemic to desert soils of the Americas.[1] Nearly two-thirds of all cases reported in the United States between 1998 and 2017 occurred among people living in Arizona. Since Arizona mandated laboratory reporting of *Coccidioides* test results in 1997, rates of reported disease have increased five-fold.[97] Possible explanations for this increase include surveillance changes, climate change, in-migration of susceptible persons, and increased disturbance of desert soils (e.g., dust storms and construction).[28]

Anthropogenic soil disturbance has long been associated with coccidioidomycosis, particularly point-source outbreaks. Half of all outbreaks reported in the literature were linked to occupational land disturbance (e.g. construction, archaeological digs, military field exercises).[52] The relationship between soil disturbance and ongoing incidence outside of outbreaks is less clear. Central and southern Arizona have undergone rapid urbanization and population growth during the last 20 years: the population of the Phoenix metropolitan area increased 87% between 1990 and 2010.[134] While urban expansion in the early twentieth century used primarily core agricultural lands, growth since 1975 has consumed native desert land. This peripheral expansion has brought populations closer to areas where desert soils are being disturbed.[135] However, the distribution of *Coccidioides* in soil is highly focal,[126] so it is plausible that the risk of infection also varies across space. Soil disturbance of native desert soils may not increase the risk of infection in all areas or the effect of disturbance may vary in magnitude across space.

We hypothesized that greater land development, measured as proportion of structures built recently and change in land cover from native desert to developed land, increased the risk

of coccidioidomycosis and that this relationship varied across the endemic area. We estimated the association between land development and census tract-specific reported coccidioidomycosis incidence in 2017 in Arizona's three most populated counties: Maricopa, Pima, and Pinal counties.

Methods

Data Sources

Records for confirmed coccidioidomycosis cases in 2017 were obtained from the Arizona Department of Health Services. Addresses for patients residing in Maricopa, Pima, and Pinal counties were geocoded using Centrus software (Pitney Bowes, Inc., Stamford, CT). These counties encompass the Phoenix and Tucson metropolitan areas, where 82% of the state's population and 95% of coccidioidomycosis cases reported in Arizona reside. Annual census tract-specific counts of reported coccidioidomycosis were calculated based on addresses that could be geocoded to the census tract-level or better.

Population denominators and sociodemographic covariates were obtained from the American Community Survey (2013–2017 five-year estimates). We selected potential confounders based on the conceptual model in Figure 5-1. These included the percent of the population 65 years of age and older (older age), the percent of the population living below the federal poverty line (socioeconomic status), and the percent of primary respondents that moved into the present housing unit after 2010 (a proxy measure for in-migration). In a sensitivity analysis, we measured in-migration using the percent of tract population moved from a different state or abroad in the past year. Rates of reported coccidioidomycosis are consistently highest among older age groups,[97] possibly due to higher prevalence of co-morbidities and greater careseeking.[71] Migrants from non-endemic areas are at risk for coccidioidomycosis due to lack of

immunity.[5] While data on socioeconomic status and risk of coccidioidomycosis are scarce, income level is strongly associated with place of residence due to economic segregation.[152] Additionally, we hypothesized that careseeking and the probability of being tested for and diagnosed with coccidioidomycosis vary by socioeconomic status. The distributions of these factors are uneven across the study area and might be associated with areas where land development occurred, particularly for in-migration.

We measured land development in two ways: (1) the percent of structures built after 2010 as recorded by the American Community Survey and (2) remotely sensed land cover change. Key land cover types (barren, shrub/scrub, developed open space, developed low intensity, developed medium intensity, developed high intensity) at 30m by 30m resolution were obtained from the 2016 National Land Cover Database.[153] We calculated remotely sensed land cover change as the percent of all pixels in a given tract that were classified as barren or shrub/scrub in 2013 and became any category of developed land in 2016. The 2013 vintage TIGER/Line® shapefiles for census tracts in Maricopa, Pima, and Pinal counties were obtained from the U.S. Census Bureau.[154]

Analysis

We limited our analysis to populated tracts with non-missing sociodemographic variables. We characterized the spatial distribution of reported cases, land cover and land cover change, and key sociodemographic covariates using exploratory spatial data analysis. A first-order queen contiguity spatial weight matrix was used for all analyses. We used choropleth maps to visualize spatial structure and qualitatively assess relationships between variables. Univariate and bivariate Moran's I, a measure of global spatial autocorrelation, were calculated to assess the presence of spatial autocorrelation and spatial correlation between variables.[155]

We hypothesized that the relationship between land development and incidence might be location-specific due to the focal distribution of the fungus in soil. Thus, we modeled the relationship between land development and census tract-specific incidence rate using Bayesian spatially varying coefficient models. This type of model allowed for the effect of land development to vary across the study area.[156] Models were specified as follows:

Equation 1.1. $Y_i \sim \beta_0 + b_{0i} + (\beta_{1+} b_{1i})X_1 + \boldsymbol{\beta X}$

where Y_i is the tract-specific case count in 2017, parameterized with a Poisson distribution, b_{0i} is the tract-specific random intercept, β_1 is the overall effect of land development, b_{1i} is the tract-specific random effect of land development, and $\boldsymbol{\beta}$ is a vector of the fixed effects of potential confounders $\mathbf{X}$. The random intercept incorporated a spatial convolution prior (i.e., a component structured by spatial adjacency and a spatially unstructured component) as in the Besag-York-Mollié model.[157] The random effect of land development incorporated a conditionally autoregressive, spatially structured component. This formulation incorporates spatial smoothing to estimate local effects by borrowing information from neighboring areas.[158] Both random effects were specified with log-gamma priors as per software package defaults.

Spatial models without the land development random effect and covariate fixed effects were used to generate smoothed rates for mapping purposes. Tract population in 2017 was included as an offset term. We used Integrated Nested Laplace Approximation to estimate the posterior distribution and marginal posterior distributions for all parameters using the R-INLA package.[159] Effects were estimated per one standard deviation increase in land development measure. Parameter distributions were summarized using posterior medians and 95% credible intervals. Estimated incidence rate ratios were calculated from the marginal posterior medians of the fixed and random effects of each land development measure. We assessed model fit using the

Deviance Information Criterion. Analyses were performed in GeoDa[160], ArcGIS (ESRI, Inc., Redlands, CA) , SAS v9.4 (SAS Institute, Inc., Cary, NC) , and R (R Core Team, 2019).

Results

There were 6,573 confirmed coccidioidomycosis cases reported in Maricopa, Pima, and Pinal counties in 2017. Of these 5,790 (88%) had address information that could be geocoded to the census-tract level or better. Cases with incomplete address information (n=783) and cases with geocodable addresses did not differ meaningfully by gender (51% vs. 49% male). The proportion of geocoded cases varied by reported county of residence: Maricopa County (89%), Pima County (86%), and Pinal County (81%). Mean age did not differ meaningfully by geocoding status (53.7 vs. 54.2 years among excluded and geocoded cases, respectively). Among 1,229 populated census tracts in the study area, 1,225 (99.7%) had complete sociodemographic covariate data; four tracts were missing the percent of the population that moved after 2010, the percent of structures built after 2010, and/or the percent of the population living below the federal poverty line.

Table 5-1 includes a description of census tract characteristics. Included census tracts ranged in land area from 0.3 to 4,731.2 km^2 (median: 2.6 km^2). A median of four cases (interquartile range: 2, 6; range: 0, 43) were reported per census tract. No cases were reported in 84 (7%) tracts. The mean percent of the tract population aged 65 years or older was 17%. The mean percent of the tract population living below the federal poverty line was 17% and ranged from 0% to 70%. The mean percent of primary respondents who moved into their present housing unit after 2010 was 54%. Across the entire study area, a majority (75%) of land cover was classified as shrub/scrub. At the tract-level, the mean percent of areas that were classified as shrub/scrub and barren land were 2% and 7%, respectively. By tract and across the study area,

the most common category of developed land cover was “developed, low intensity” (mean percent of tract area: 31%). Between 2013 and 2016, a mean of 1.5% of tract areas changed land cover categories (median: 0.3%; IQR: 0.1%, 1.1%); there was no land cover change in 142 (12%) tracts. The mean percent of tract area that changed from shrub/scrub or barren during this time period was 0.27% (median: 0%; IQR: 0.0%, 0.12%). Change from barren to developed land was more common than change from shrub/scrub to developed land (mean: 0.26% vs. 0.008%). The mean percent of tract structures built after 2010 was 3.3%.

Tract-level incidence rates were non-uniform across the study area. Figure 5-2a displays spatially smoothed incidence rates by census tract. The estimated median incidence rate was 91 reported cases per 100,000 person-years (IQR: 73, 117). Smoothed rates were highest in tracts along the periphery of the Phoenix metropolitan area (Maricopa County), particularly the northern and southeastern edges, and the northern, northeastern, and southwestern edges of the Tucson metropolitan area (Pima County). Urban cores (e.g., Central Phoenix) and large rural tracts had lower rates. The Moran’s I statistic for the raw tract incidence rate was 0.20, indicating positive spatial autocorrelation of incidence. Land development measures were also distributed unevenly across the study area (Figures 5-2b–2c). The percent of structures built after 2010 was lowest in the urban core tracts of both metropolitan areas and higher in suburban and peri-urban tracts of the Phoenix metropolitan area and the northern and southern extremes of the Tucson metropolitan area. Tracts with higher percent of tract area that changed from barren or shrub/scrub to developed formed a ring around both metropolitan areas; several tracts in Pinal County also had higher than average remotely sensed land development. Remotely sensed land development between 2013 and 2016 appeared to be more concentrated and focal than the

percent of structures built after 2010. Spatial distributions of potential confounders are summarized in Supplemental Figures 5-S1–S4.

In the bivariate analysis, the bivariate Moran's I for raw incidence rate and land development were 0.04 for the percent of structures built after 2010 and 0.05 for the 2013 to 2016 percent change from barren or shrub/scrub to developed, indicating zero-to-negligible positive spatial correlation. Among sociodemographic covariates, the bivariate Moran's I statistic for raw rate and the percent of the tract population 65 years or older was strongest (0.23), followed by the percent below poverty (-0.16), and the percent moved after 2010 (-0.03).

Results from spatially varying coefficient models are summarized in Table 5-2. A standard deviation increase in remotely sensed land development was associated with a 1.07-fold higher incidence rate (95% CrI: 1.01, 1.07). A standard deviation increase in the percent of structures built after 2010 was associated with a 1.07-fold higher incidence rate (95% CrI: 1.03, 1.10). Tract-specific estimates for both land development measures showed near-zero variability across census tracts. Unadjusted and adjusted associations between land development measures and incidence rates did not differ substantially (not shown). Results from the sensitivity analysis measuring in-migration using the percent moved from a different state or abroad in the past year were similar.

Discussion

In this study of census tract-level land development and coccidioidomycosis incidence, we found a weak association between greater land development and higher rate of reported coccidioidomycosis. Contrary to our hypothesis, the relationship between land development and incidence rate did not vary across space. Tract-specific rates of reported coccidioidomycosis varied substantially across the study area. Rates were spatially correlated with the percent of the

population 65 years and older and inversely associated with the percent living below the poverty line. While there was measurable land cover change in the majority of tracts between 2013 and 2016, conversion of barren or shrub/scrub land to developed land occurred in only approximately half of all tracts.

Several studies have examined the relationship between land development and coccidioidomycosis in Arizona. Blair et al. compared the one-year risk of coccidioidomycosis in employees at a healthcare facility adjacent to a construction site with workers at another facility located elsewhere in the Phoenix metropolitan area. An in vitro lymphocyte-activation assay was used to measure cellular immunity to coccidioidomycosis, allowing for measurement of asymptomatic infections. Contrary to their hypothesis of increased risk of infection at the site adjacent to construction and excavation of native desert soil, the author found a higher risk of infection at the control site.[47] Park et al. mapped 1998–2001 age-adjusted incidence rate in Maricopa County and noted high rates in areas undergoing construction and development along the periphery of metropolitan Phoenix. There was no association between monthly coccidioidomycosis case reports and number of building permits issued in Maricopa County between 1998 and 2001.[65] However, issue dates of building permits do not necessarily coincide with construction and soil excavation. Building permits are also issued for a variety of activities, not all of which involve soil excavation. This analysis did not account for the location for which the permit was issued (e.g., native desert area vs developed land) and the location of incident case reports. Finally, Pianalto et al. examined the relationship between construction-related soil disturbance, which was estimated from fugitive dust emissions estimated from remote sensing data, and lagged incidence between 1995 and 2006 in Pima County. At the county-level, annual construction-related disturbance and lagged incidence were highly correlated. Analyzed by ZIP

code, there was modest correlation between total incidence during the entire study period and disturbance in ZIP codes at the periphery of Tucson and no correlation at inner or core Tucson metropolitan area ZIP codes.[161]

Rapid suburban expansion has been hypothesized to contribute to increasing reports of coccidioidomycosis in Antelope Valley, an area north of Los Angeles abutting the hyperendemic area in California. Colson et al. examined the correlation between 2000 and 2015 coccidioidomycosis incidence and land disturbance in this area. Land disturbance was significantly associated with incidence, although the magnitude of the adjusted effect was very small.[137] Guevara et al. found that the number of reported new residential buildings in Antelope Valley was correlated with coccidioidomycosis incidence rate in Los Angeles County between 1996 and 2007; construction outside of Antelope Valley was not strongly correlated with incidence. While construction has decreased since 2005, incidence rates have not consistently declined since then.[138]

This ecologic study has several limitations. We used a year of incident case reports as a proxy for risk of infection, and results cannot be extrapolated to individual-level risk. Additionally, cases were aggregated to their census tract's centroid. The choice of spatial scale and unit of aggregation can have a significant impact on estimates. Brown et al. examined the association between several areal characteristics and incidence for 2006–2009 cases in Arizona at the case residence, block group, tract, and ZIP code scales. Factors associated with incidence across scales included population 65 years or older, median income, soil organic carbon, medium and high intensity developed, pasture/hay, and distance to desert. However, associations with shrub/scrub land, cultivated crops, and distance to wetland varied in magnitude and/or direction by spatial scale.[68] The spatial distribution of *Coccidioides* growth sites might exhibit variability

at a scale much smaller than the 30-meter resolution of LandSat imagery.[162] Thus, risk of infection likely varies at smaller spatial scales than a census tract. We were unable to model incidence at scales below the census tract due to the lack of population sociodemographic data at these levels for intercensal years. The temporal resolution of our land development measures and incidence estimates may also have been too coarse to capture short-term increases in cases associated with nearby soil disturbance.

We attempted to control for in-migration of susceptible persons and differences in census tract demographic composition. However, we ignored uncertainty in American Community Survey estimates and assumed estimates from surveys continuously conducted between 2013 and 2017 accurately represented the population in 2017. Methods to incorporate sampling error in spatial Bayesian hierarchical models are not readily available. Imprecise or erroneous confounder measurement might result in incomplete or absent control for confounding.

Overall, we observed marked heterogeneity in census tract incidence rate of coccidioidomycosis. However, the determinants of this spatial distribution remain unclear. Fine-scale measurement of fungal activity—for example, using recent advances in detection of airborne *Coccidioides*[21]—would improve our understanding of the effect of soil disturbance on risk of infection. Longitudinal studies incorporating such improved measures and multiple years of incidence data might help elucidate the relationship between land development and incidence.

Figure 5-1. Directed acyclic graph for the relationship between land development and coccidioidomycosis incidence

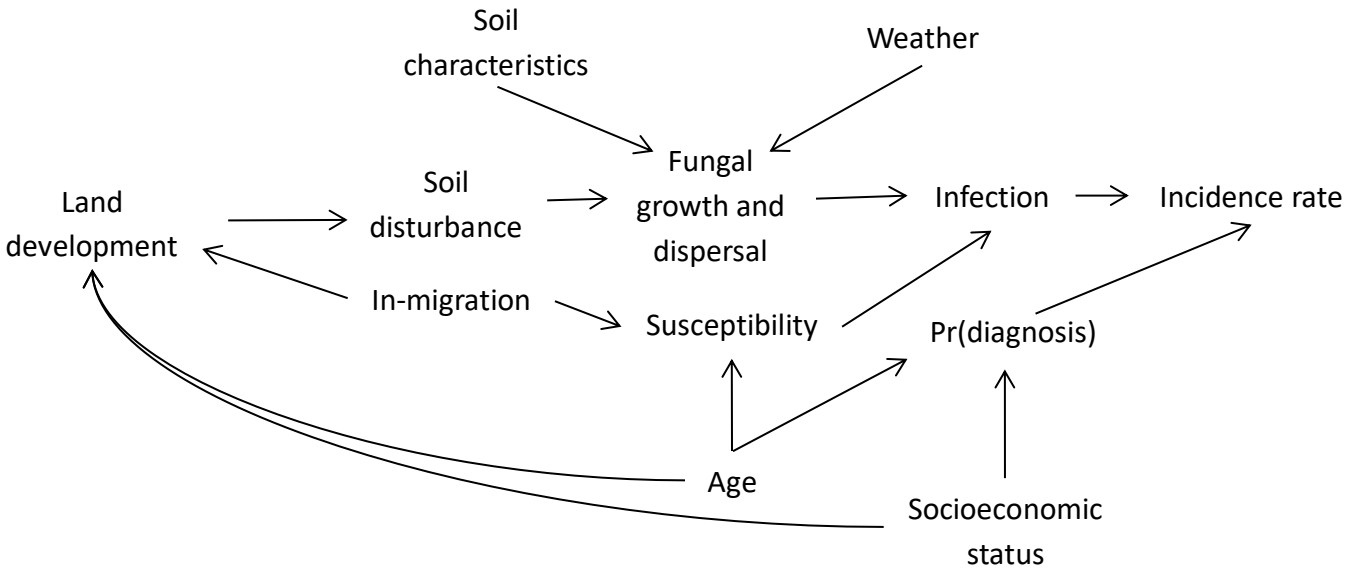
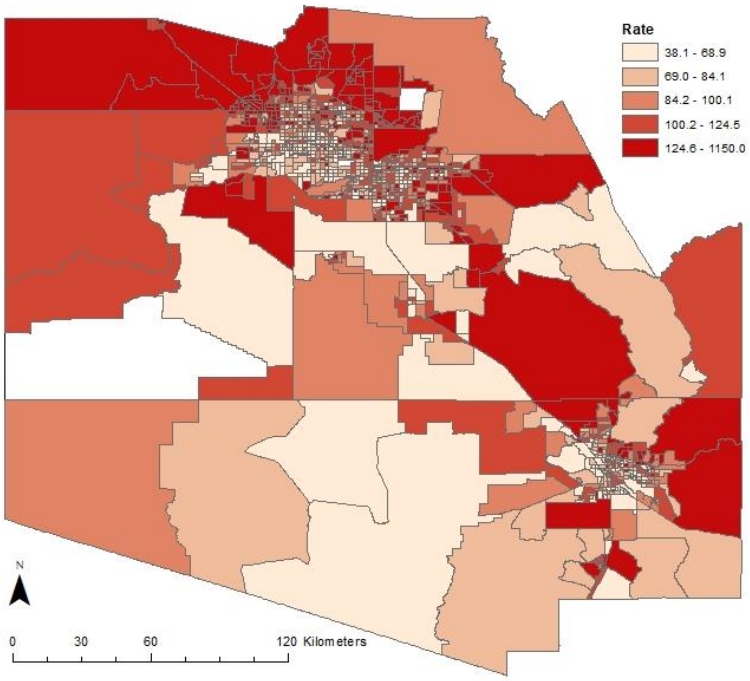
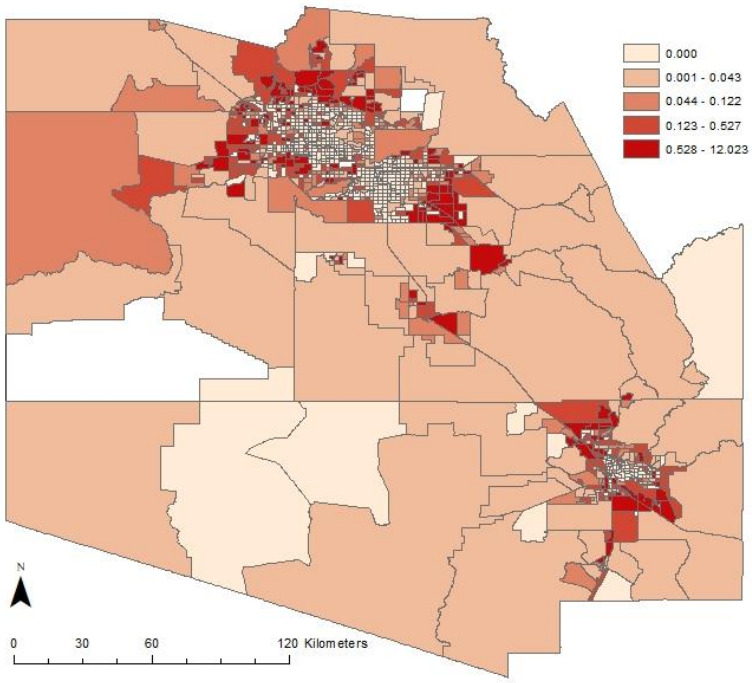


Figure 5-2a–c. Choropleth maps of census tract rate of reported coccidioidomycosis and land development measures by quintile

(a) Spatially smoothed rate of reported coccidioidomycosis in 2017



(b) Census tract-specific percent of land area changed from shrub/scrub in 2013 to developed land in 2016



(c) Census tract-specific percent of structures built after 2010

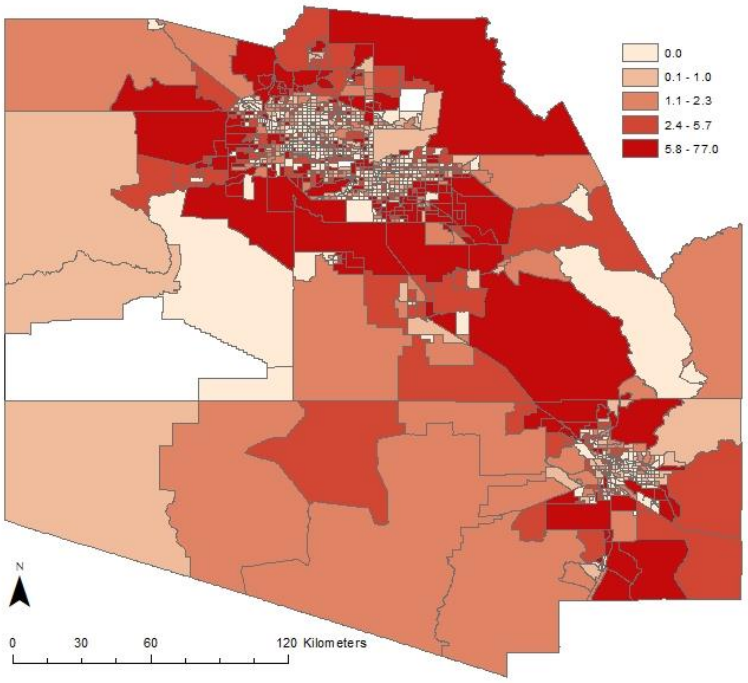


Figure 5-S1. Choropleth map of census tract percent of the population aged 65 years or older by quintile, 2017

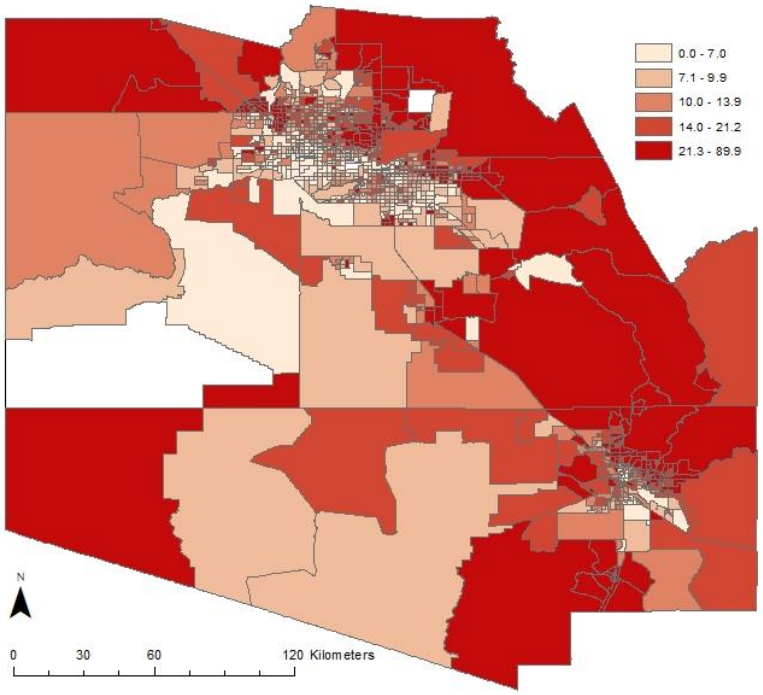


Figure 5-S2. Choropleth map of census tract percent of the population living below the federal poverty line by quintile, 2017

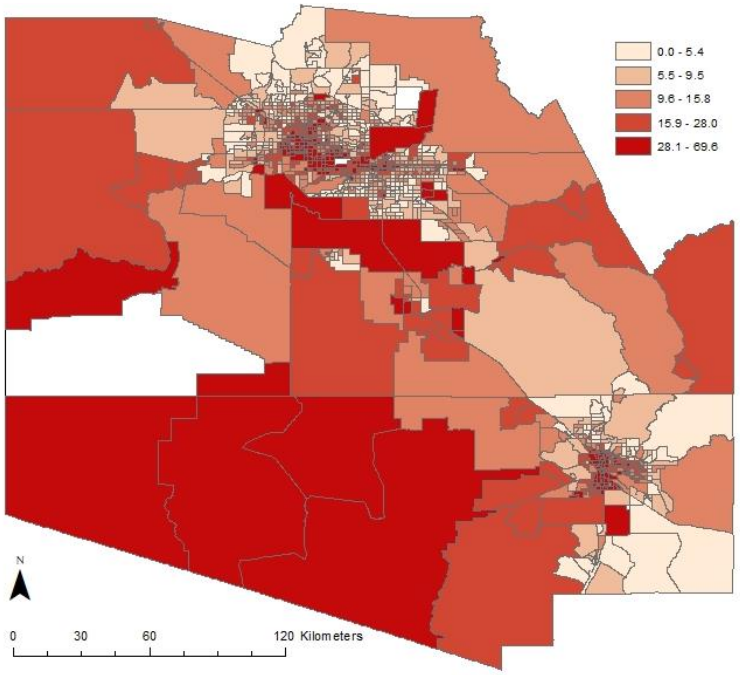


Figure 5-S3. Choropleth map of census tract percent of the population moved to present housing unit after 2010 by quintile, 2017

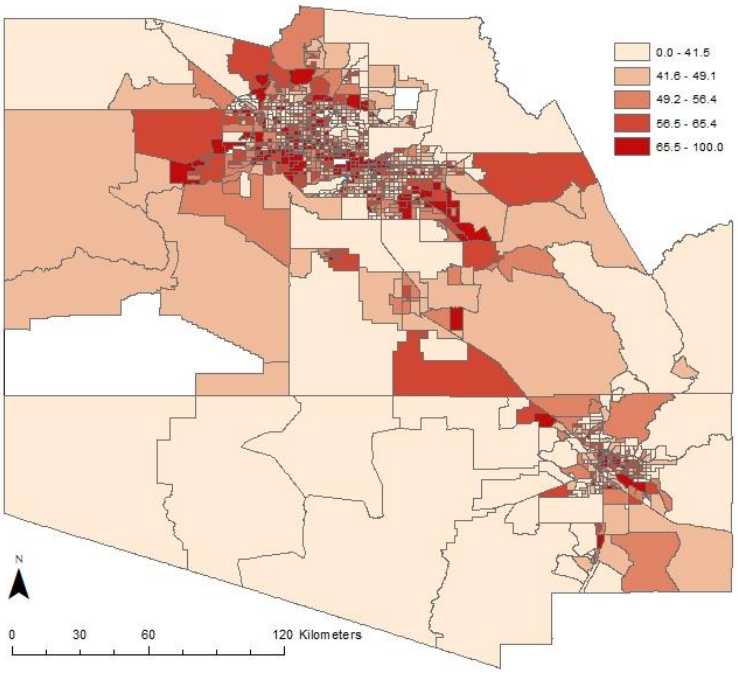


Table 5-1. Descriptive characteristics of included census tracts in Maricopa, Pima, and Pinal counties

	Mean (SD)	**Median (IQR)**
Land area (km^2)	4.7 (3.0)	2.6 (2.0–5.6)
Population	4,538 (1,977)	4,302 (3,118–5,593)
% 65+ years old	16.5 (15.7)	11.7 (7.7–18.5)
% living below the federal poverty line	16.6 (13.1)	12.5 (6.4–24.6)
% moved into present unit after 2000	82.0 (11.6)	53.0 (74.2–90.8)
% moved into present unit after 2010	53.5 (14.0)	53.1 (44.0–62.8)
% moved from different state or abroad in the past year	4.3 (3.5)	3.5 (1.8–5.9)
Incidence		
Reported coccidioidomycosis cases	4.7 (4.2)	4 (2–6)
Spatially smoothed incidence rate (per 100,000 person-years)	104.2 (59.4)	91.1 (73.0–117.4)
Land Cover		
% developed, open space (2016)	25.0 (15.0)	25.0 (12.1–36.3)
% developed, low intensity (2016)	31.0 (17.3)	32.2 (17.8–43.9)
% developed, medium intensity (2016)	12.7 (13.7)	7.5 (2.6–18.6)
% developed, high intensity (2016)	5.4 (10.7)	1.1 (0.1–6.1)
% shrub/scrub (2016)	1.6 (8.9)	0 (0–0)
% barren (2016)	7.1 (15.6)	0.5 (0–4.2)
% change in land cover category, 2001 to 2016	13.4 (17.5)	6.4 (2.8–15.5)
% change in land cover category, 2011 to 2016	1.2 (2.6)	0.3 (0.1–1.1)
% change in land cover category, 2013 to 2016	1.5 (2.5)	0.3 (0.1–1.1)
Land Development		
% structures built after 2000	27.1 (29.2)	14.0 (5.1–39.7)
% structures built after 2010	3.3 (6.1)	1.0 (0–3.7)
% shrub/scrub in 2013 developed in 2016	0.008 (0.062)	0 (0–0)
% barren in 2013 developed in 2016	0.259 (0.854)	0 (0–0.118)
% barren or shrub/scrub in 2013 developed in 2016	0.266 (0.872)	0 (0–0.122)

Table 5-2. Adjusted incidence rate ratios for the associations between land development measures and reported coccidioidomycosis incidence in 2017

	Adjusted*			**Sensitivity Analysis****		
	Fixed effect (β_1)	Tract-specific estimate	DIC	Fixed effect (β_1)	Tract-specific estimate	DIC
	Median rate ratio (95% CrI)	Median rate ratio range		Median rate ratio (95% CrI)	Median rate ratio range	
% barren or shrub/scrub in 2013 to developed in 2016	1.04 (1.00, 1.07)	1.03, 1.04	5,459	1.04 (1.00, 1.07)	1.04, 1.04	5,462
% structures built after 2010	1.07 (1.03, 1.10)	1.07, 1.07	5,455	1.07 (1.04, 1.11)	1.07, 1.07	5,457

Abbreviations: CrI - credibility interval

*Adjusted for percent below poverty line, percent 65 years or older, and percent moved into present unit after 2010

**Adjusted for percent below poverty line, percent 65 years or older, and percent moved from different state or abroad in the past year

Table 5-S1 Unadjusted associations between potential confounders and census tract-specific rate of reported coccidioidomycosis in 2017

	Median rate ratio (95% CrI)
% 65+ years old	1.02 (1.02, 1.02)
% living below the federal poverty line	0.98 (0.98, 0.98)
% moved into present unit after 2010	0.99 (0.99, 0.99)
% moved from different state or abroad in the past year	1.03 (1.01, 1.04)

CHAPTER 6: CONCLUSIONS AND FUTURE DIRECTIONS

Collectively, the studies in this dissertation add several novel findings to the literature on coccidioidomycosis epidemiology. I examined the possible roles of surveillance changes, weather, and land use in explaining trends in coccidioidomycosis incidence in Arizona. To date, studies of coccidioidomycosis have largely ignored changes in surveillance methodology. These changes have hindered our understanding of the disease not only in Arizona, but also nationally, given that a majority of case reports occur among Arizona residents. In Chapter 3, I used probabilistic bias analysis to estimate trends in coccidioidomycosis incidence in Maricopa and Pima counties. I created annual bias-adjusted estimates of reported confirmed case counts. On average, incidence rates increased between 1998 and 2017, even after adjustment for surveillance changes. Notably, rates remained elevated between 2009 and 2012. Changes in the age and sex distribution of reported cases were partly attenuated for by bias adjustment.

These estimates may serve as a baseline against which future increases in case reports could be compared. Estimates could also be used by other researchers and public health agencies for future studies of coccidioidomycosis incidence. This analysis could serve as a model for analysis of infectious disease incidence trends when surveillance methods have not been consistent over time. Changes in diagnostics and electronic disease surveillance systems are common and have affected surveillance for other infectious diseases (e.g., the introduction of culture-independent tests for foodborne diseases[142]). Other methods such as Bayesian hierarchical modeling[163] to adjust for surveillance changes are more complex and not as accessible to health department staff.

New and emerging diagnostics for coccidioidomycosis such as the recently introduced lateral flow assay[141] are likely to affect the sensitivity and specificity of surveillance. Public health agencies can anticipate and prepare for these changes by planning to conduct studies to

assess their impact and maintain consistent time series of reported case counts. Surveillance informatics systems should allow for the prospective collection of reporting laboratory, ordering provider and test type for each quantitative and/or qualitative test result as part of routine surveillance (e.g., via electronic laboratory reporting) in an analyzable fashion. Surveillance would also benefit from routine surveys of reporting laboratories to ascertain which tests and test kits are being currently being utilized. As surveillance for coccidioidomycosis is laboratory-based in Arizona and California, laboratory characteristics of reported cases should be routinely analyzed and monitored for changes over time. Telephone-based interviews of random samples of cases ('enhanced surveillance') are often conducted by state and local health departments[164] including in Arizona[75], to better understand patient characteristics and disease burden. Sampling for these studies should be stratified by laboratory characteristics to allow for more efficient study of variation in patient characteristics (e.g., disease severity, time to careseeking and testing) by laboratory test results. Previous enhanced surveillance studies[75] have validated Arizona's laboratory-based case definition by assessing what proportion of cases met the clinical criteria of the national case definition (i.e., the positive predictive value of a laboratory-only case definition). Estimating the positive predictive value by laboratory characteristic (e.g., isolated EIA positive vs. EIA positive with positive immunodiffusion) could help refine the case definition and improve the specificity of surveillance.

Health agencies should consider partnerships with reference laboratories and local healthcare systems to routinely collect measures of careseeking and testing for coccidioidomycosis. Crucially, these data could include patients who test negative for the disease, providing further insight into testing practices and more specifically, the potential impact of decreases in surveillance specificity. These partnerships would provide a platform

from which to design and conduct validation studies, such as the EIA reproducibility study[113] used in Chapter 3, and generate estimates for bias adjustment in the event of a surveillance change.

In Chapter 4, I used the bias-adjusted estimates from Chapter 3 to analyze the relationships between weather and coccidioidomycosis incidence in Maricopa and Pima counties. Seasonally-adjusted long-term trends in incidence were visually concordant with trends in total precipitation, average wind speed, and PM_{10}. Lagged winter precipitation and late summer average temperature were positively correlated with subsequent incidence in both counties. These findings are consistent with previous studies in Arizona. Correlations with lagged average wind speed and incidence have not been previously reported. Lagged PM_{10} was negatively correlated with incidence. I also examined and attempted to address methodologic issues with the literature on the environment and coccidioidomycosis. In addition to utilizing one of the longest time series of coccidioidomycosis incidence analyzed to date, I compared results using routine and bias-adjusted case counts; previous studies have used data affected by surveillance changes without adjusting for potential biases. Additionally, few studies have used multiple analytical methods on a single dataset and thus, results are difficult to interpret and compare across studies. However, the findings from this study suggesting that bias adjustment may not be necessary for future studies. I also found that aggregating case reports and environmental variables into meteorological seasons produced concordant results with analyses at the monthly level.

Multivariable prediction models did not produce high accuracy one-month-ahead forecasts of monthly coccidioidomycosis incidence rate in either county. However, accurate forecasts would require models that explain an exceptionally high proportion of variance in

incidence. To date, this has not been achieved by any of the previous quantitative studies relating weather to coccidioidomycosis incidence. Forecasting might be inherently limited by stochasticity of weather, the heterogeneity of case reports, particularly variation in time from exposure to report, and incomplete ascertainment of infections. Instead of forecasting, public health agencies might benefit from an aberration detection approach. This would involve defining the average coccidioidomycosis season and developing quantitative thresholds to define meaningful departures from the baseline. Detecting a severe season during the earlier months of the annual increase in incidence could guide the timing of public health messaging for the general public and healthcare providers.

Recent advances in detection of *Coccidioides*[21] DNA in air samples allow for more advanced studies of *Coccidioides* ecology and the exposure biology of coccidioidomycosis in endemic areas. Preliminary proof-of-concept air sampling studies have found spatial and temporal differences in the presence and concentration of arthroconidia across a network of air sampling stations.[22] This network could be leveraged for studies of the relationship between weather and *Coccidioides* by co-locating environmental sensors to measure temperature, rainfall, wind speed, PM_{10}, and other parameters. These studies could exploit the fine-scale heterogeneity in *Coccidioides* activity and weather (e.g., uneven distribution of precipitation) to elucidate the relationships between the two.

This work should be complemented by field studies using air sampling and environmental measurements (including small mammal activity, and soil moisture and temperature at multiple depths) at *Coccidioides* growth sites in native desert areas. A critical missing piece in the literature is a mechanistic explanation for the lagged relationships between environmental parameters (e.g., precipitation) and incidence; time between exposure and case

report does not account for the one- to two-year lagged relationships observed in this study and by others.[133] Field studies could help fill in this gap and define the biological plausibility of long-term lagged relationships. Identifying a more widely measured correlate of airborne arthroconidia such PM_{10} would also be of great value to public health agencies.

Relating arthroconidia presence and concentration to human infections will be more challenging. At present, the viability and infectiousness of sampled arthroconidia has not been assessed (i.e., by culture or inoculation of laboratory animals). Moreover, no epidemiologic studies establishing whether concentration is linked or proportional to risk of infection have been conducted. There are several possible designs for such studies. An ecologic longitudinal analysis of census tract incidence rates and lagged modeled local arthroconidia concentration (e.g., using kernel density methods) would be a first step and could help identify a link between air sampled concentration and risk of infection.

Prospective cohort studies of individuals are a stronger design, but assembling a geographically dispersed cohort of susceptible persons would be very challenging because (1) past studies suggest high prevalence of immunity, (2) assessing immunity requires the use of a cumbersome skin test or a research laboratory-based assay, both with poorly defined performance characteristics in asymptomatic persons, and (3) the annual risk of infection is thought to be relatively low, necessitating large sample sizes. Special populations such as newly arrived military personnel, extensively studied in early seminal studies of coccidioidomycosis, or recent migrants to the endemic area could serve as a natural cohort. Performing such a study in animals (e.g., a cohort of puppies[165]) would also be feasible. Finally, it might be possible to compare genotypes of environmental strains, using metagenomics or sequencing of air sample-derived isolates, to isolates collected from human or animal cases. As nearly all sequenced

isolates, human and environmental, are unique genotypes, a match between an environmental isolate and a clinical isolate would provide evidence to support the link between the presence of fungal DNA in an air sample and human infections.

In Chapter 5, I examined the relationship between soil disturbance, operationalized as remotely sensed conversion of desert into developed land and recent building year of structures, and census tract rate of reported coccidioidomycosis. This is the first study to use Bayesian spatial regression methods to model coccidioidomycosis and produce small-area estimates of incidence. I hypothesized that greater land disturbance would be associated with higher incidence, and the magnitude of this effect would vary across the study area (Maricopa, Pima, and Pinal counties), given the focal distribution of *Coccidioides* in soil. A weak positive association between soil disturbance measures and incidence was observed, with no spatial variation of the effect.

Future studies of this relationship would benefit from a longitudinal design estimating the effect of soil disturbance on change in census tract incidence rate. Natural experiments might also be conducive to estimating this effect. A previous study examined the prevalence of immunity to coccidioidomycosis among healthcare workers at a facility adjacent to a construction site and a control facility where construction did not take place.[47] This design could be adapted to an area-level analysis of residential communities adjacent to suburban development of native desert. While it would be prohibitively expensive to conduct largescale serosurveys, rates of reported confirmed cases serve as an approximation of incidence. Patients might be more likely to spend time outdoors near their place of residence and thus, residential location might be a better measure of exposure.

There was marked heterogeneity in census tract incidence rate across the study area, with strong evidence of spatial patterning of incidence. Rates were higher in the peripheries of metropolitan Phoenix and Tucson. Higher rates were observed in tracts where a greater proportion of the population was over 65 years old while rates were inversely associated with census tract poverty level. These associations are unexplained and merit further study. Future analyses should include additional area-level sociodemographic predictors (e.g., health insurance, occupation class) to identify predictors of incidence. As place of residence represents only one site of exposure, developing other measures to capture spatial behavior, mobility patterns, and cumulative exposure to airborne arthroconidia would be useful.

Exposure has only been described in detail for cases associated with outbreaks (mostly point-source) and may not be generalizable to cases that occur during annual community-wide epidemics in Arizona. This represents a major gap in our understanding of how most people are exposed to *Coccidioides*. One possible approach is to collect activity space information: online mapping-based instruments allow subjects to geo-locate visited locations and describe the duration and frequency of visits.[166] Ideally, one would estimate the relationship between particular spatial behaviors and risk of infections in cases and susceptible controls. As noted above, identifying controls would be quite challenging. However, it might still be informative to compare the spatial behaviors of matched control residents (regardless of immune status) and cases in high and low incidence areas.

As noted in Chapter 1, migration of susceptible persons into endemic areas might have contributed to the increasing incidence of reported coccidioidomycosis. The populations of highly affected counties have grown substantially during the study period, primarily due to in-migration. This hypothesis requires investigation, yet few studies have examined this

phenomenon. Retrospectively estimating the contribution of in-migration to trends in incidence is difficult because of the unmeasured and unknown effects of weather and careseeking and/or testing practices. Additionally there are no data sources to estimate annual in-migration and out-migration by immune status. Future studies could quantify the risk of infection (symptomatic only or overall) in a cohort of recent in-migrants (e.g., students, military personnel, retirees).

I examined several possible explanations for the large increase in rates of reported coccidioidomycosis between 1998 and 2017. My analyses decomposed temporal trends into shorter- and longer-term components and considered their causes accordingly. Drivers of long-term components (e.g., the linear increase prior to surveillance changes) remain unknown. While surveillance changes dramatically affected reported case counts after 2009, artifacts do not appear to explain the long-term trend or all peaks in reported cases. Weather is a probable explanation for short-term increases (e.g., 2011). The longer-term components were unlikely to be related to weather as corresponding changes in weather were not observed. The role of land development in temporal trends has yet to be established.

Conducting trend analyses at smaller spatial resolutions might provide additional insights. The surveillance change and weather studies aggregated data at the county-level. The land development study used census tract as the unit of analysis, but lacked a time component. The interacting dynamics of weather, fungal growth and dispersal, soil disturbance, and behaviors of susceptible persons are no doubt heterogeneous at sub-county scales and might affect incidence at differing temporal horizons. Future studies should exploit spatiotemporal differences and jointly collect multi-year data on these factors at smaller spatial and temporal scales to elucidate their relative contributions to incidence. These findings might help public

health agencies develop and target interventions to reduce the risk of infection and mitigate the burden of disease.

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