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Sociodemographic Factors Associated with Patients Hospitalized for Coccidioidomycosis in California and Arizona, State Inpatient Database 2005-2011

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Abstract

Sociodemographic Factors Associated with Patients Hospitalized for Coccidioidomycosis in California and Arizona, State Inpatient Database 2005-2011

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Background: Coccidioidomycosis is endemic in the Southwestern United States. Disseminated infection can be life-threatening and is responsible for hospitalization and healthcare resource utilization. There are limited data evaluating factors associated with coccidioidomycosis hospitalization.

Methods: We conducted a cross-sectional study to assess sociodemographic and comorbidity factors associated with hospitalization due to coccidioidomycosis in California and Arizona compared to hospitalization for other causes. We analyzed hospital discharge data obtained from the State Inpatient Dataset (SID) for both California and Arizona for years 2005-2011. Multivariable logistic regression modeling was used to analyze factors associated with coccidioidomycosis.

Results: A total of 23,758 hospitalizations due to coccidioidomycosis occurred during the study period in the two states. Arizona had an over six-fold higher coccidioidomycosis hospitalization incidence rate compared to California, 198.9 vs 29.6/per 100,000-person years. In the multivariable model patients aged (40-49) years had a higher odds of hospitalization due to coccidioidomycosis vs young adults (18-29) years (aOR=1.50 [95% CI 1.43-1.59]). African Americans had higher odds of hospitalization due to coccidioidomycosis vs. Caucasians (aOR= 1.98 [95% CI 1.89-2.06]). Residing in a large rural town had a higher odds of hospitalization due to coccidioidomycosis vs residing in an urban area (aOR=2.28 95% [CI 2.19-2.39]). Higher comorbidities were associated with an increased odds for hospitalization due to coccidioidomycosis (aOR=1.02 [95% CI 1.02-1.03]) for each point in the Elixhauser score). Uncomplicated diabetes and chronic pulmonary disease was also associated with hospitalization due to coccidioidomycosis (aOR=1.47 [95% CI 1.41-1.52] and (aOR=1.59 [95% CI 1.54-1.65]), respectively.

Conclusions: We found sociodemographic factors and comorbidities associated with hospitalizations due to coccidioidomycosis compared to hospitalization due to other causes. Identifying persons at highest risk for hospitalization with coccidioidomycosis may be helpful for future prevention efforts.

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Introduction

Coccidioidomycosis also known as San Joaquin Valley Fever or Valley Fever is a fungal infection caused by the inhalation of *Coccidiodes spp*. spores and is a common cause of community-acquired pneumonia in the Southwestern United States [1]. Although the majority of patients typically experience a self-limiting disease course, approximately 1% of patients diagnosed with coccidioidomycosis will develop disseminated disease [2]. Disseminated coccidioidomycosis can be life-threatening and is associated with a significant degree of morbidity and mortality. Moreover, it constitutes a financial burden for hospitals due to prolonged hospital stays and expensive and often lifelong treatment options for this patient population [3]. The objective of this study is to investigate the relationship between epidemiological and sociodemographic factors among patients who were hospitalized with coccidioidomycosis in two highly endemic states, California and Arizona. We hypothesize that patients hospitalized due coccidioidomycosis experience an increased morbidity and possess a unique set of sociodemographic characteristics. We further hypothesize that hospitalizations and high morbidity or mortality related to coccidioidomycosis are related to sociodemographic characteristics such as race, as has been demonstrated by Luo et al. [3]. The results of this study will aid in the identification of populations at higher risk for coccidioidomycosis hospitalization. Furthermore, the proposed epidemiological study will contribute to the current knowledge base for hospital admitted coccidioidomycosis patients, potentially improving health care delivery for this inpatient population.

Historical perspective

The first physician credited with describing a case of coccidioidomycosis was Alejandro Posadas in 1892 (1870-1902) [4]. Alejandro Posadas was a medical intern at the University of

Buenos Aires when he documented his clinical observations of coccidioidomycosis in one of his patients. His patient, Domingo Ezurra, a member of the Argentine army, presented with a massive purple, fungal-like mass on the right side of his face and several papules on his extremities [5]. Microscopic evaluation of skin samples taken from Domingo Ezurra revealed *Coccidia*-like protozoan organisms [4-5]. Soon after Dr. Posadas' assessment of the clinical presentation of coccidioidomycosis, other physicians in central California were also observing clinical cases of coccidioidomycosis. Consistent with the early classification of the causative agent of coccidioidomycosis as a protozoan organism, Dr. Emmet Rixford from Cooper Medical College in San Francisco and a group of physicians from Johns Hopkins Medical School, T. Caspar Gilchrist and CW Stiles, collectively agreed that an organism isolated from similar skin lesions was a protozoan. The skin lesions were taken from a migrant worker who worked as a farmer in the San Joaquin Valley of California. The protozoan was given the name *Coccidioides immitis* [6]. The origin of the name is based on the organism's morphologic appearance and clinical feature, *Coccioides* ("resembling Coccidia") and *immitis* ("not mild") [6]. In 1900 *C. immitis* was reclassified as a fungus by Drs. William Ophuls and Herbert C. Moffitt [7].

In 1929, a Stanford University Medical School student, Harold Chope, studying *C. immitis* in the laboratory of Dr. Ernest Dickson accidently inhaled *Coccidioides spp*. spores. He subsequently developed a nonfatal pulmonary illness and erythema nodosum. As a result of his clinical presentation, and the fact that he inhaled *C. immitis* spores, a connection was made: *C. immitis* was the causative agent of San Joaquin Valley Fever [6].

Dr. Charles Smith, an early physician scientist whose research focused on coccidioidomycosis in both Kern and Tulare counties of California, contributed to a better understanding of the epidemiological features of the disease. He recruited patients with

suspected cases of San Joaquin Valley Fever by contacting local health departments and physicians working in the area as well as local labor camps [7]. The results of these studies determined that the incubation period for the disease is between 1 and 3 weeks [7]. Additionally, Dr. Smith characterized the immunological response of the disease by performing skin reactivity test on his study participants [7]. Dr. Smith is also credited with determining that the transmission of coccidioidomycosis is not by person to person transmission [7].

Pathogen lifestyle and characteristics

Coccidioidomycosis is caused by members of the *Coccidioides spp*. *Coccidiodes spp*. are dimorphic fungi with two distinct life cycle phases. [8]. In the soil, *Coccidioides spp*. exists in a saprophytic phase consisting of mycelia while within susceptible mammalian hosts, *Coccidsoides spp.* exists in a parasitic phase [9]. *Coccidioides ssp*. are found in the Western Hemisphere, within warm, arid desert regions [8]. Additionally, *Coccidioides spp*. reside 10-50 cm beneath the surface of sandy soil that is typically alkaline [8]. Two species of *Coccidioides*, C. *posadasii* and *C. immitis*, have been identified as the causative agent of coccidioidomycosis; however, their geographical distribution varies [10]. *C. immitis* is found in Central and Southern California regions, with the San Joaquin Valley being an area of highest endemicity [10]. *C. posadasii* is highly endemic to Central and Southern Arizona but is also found in Western Texas, Southern New Mexico, Mexico and Central and South America [10]. Research has shown that there is approximately a 5% genomic variation between *C. posadasii* and *C. immitis* [11].

Within the soil, *Coccioides spp*. exists as a mold with septate hyphae [12]. Fungal growth has been shown to be influenced by environmental climate changes [12]. Seasonal variation in precipitation levels contribute to the fungal growth patterns. Moist soil allows the fungus to grow while dry conditions facilitate arthroconidia formation. Upon soil disruption, the

hyphae separate into individual arthroconidia and become airborne [12]. If arthroconidia are inhaled by a susceptible host, morphological changes will occur in the terminal bronchiole. Susceptible hosts include humans and both domestic and non-domestic animals; however, no zoonotic transmission to humans has been reported to date and the organism is not transmitted from human to human [13]. However, organ donor-derived coccidioidomycosis transmission has been reported in endemic areas [14]. During the early stages of infection, the inhaled arthroconidia become spherules which will eventually fill with endospores after numerous cell divisions. If the spherules rupture, the endospores are released and subsequently extrapulmonary dissemination to other host tissues or organs can occur [2].

Pathogenesis

Several factors have been associated with the virulence mechanisms of *Coccioides spp.* Theses mechanisms include both evasion and manipulation of host innate and adaptive immune responses. Phagocytosis of mature spherules by polymorphonuclear leukocytes (PMNs) is limited due to their size and their hyphal outer wall layer that is retained during the early transformation process from inhaled arthroconidia to spherules [15]. Additionally, the fungus produces enzymes that disrupt host immune responses such as proteases, and ureases [16].

During the parasitic phase of *Coccidioides spp,* infection several pathogen associated Pattern Recognition Receptors (PRRs) present on innate immune cells facilitate recognition of spherules and endospores. These PRRs include Toll-like receptors (TLRs), C-Type lectin receptors (CLRs), NOD-Like receptors (NLDs), and Rig-I like receptors [17-18]. Research has shown that TLR-2 is responsible for the initial recognition of spherules while TLR-4 may play a role in preventing the extrapulmonary dissemination of C*occidioides spp*. [18]. Activation of innate immune cells results in production of pro-inflammatory cytokines such as interferon-

gamma, interlukin-23 and Il-1B. This in turn guides the differentiation of Th1 and Th17 T-cells. Th1 and Th17 T-cells have been shown to facilitate protective T-cell immunity during C*occidioides spp*. infection [18]. Approximately 60% of coccidioidomycosis cases are asymptomatic while the remaining 40% develop symptomatic self-limiting respiratory infection. Of the patients that develop symptomatic respiratory infection, approximately 5% experience extrapulmonary infection [9]. Infection with *Coccidioides app* results in long-lived protective cellular immunity in the majority of infected individuals [19].

Coccidioidomycosis clinical presentation and course

The clinical manifestations associated with coccidioidomycosis vary considerably and exist on a spectrum ranging from mild to severe disease. The spectrum of clinical syndromes includes initial pulmonary infection to an array of pulmonary and extrapulmonary complications, with coccidioidal meningitis being the most severe clinical manifestation [20]. The driving forces responsible for this variability is multifactorial. Factors such as, host genetic background, the status of the host immune system, organism inoculum size, presence of virulence factors and whether or not the organism possess antibiotic resistance genes have been suggested as key factors influencing illness severity [21]. Early and accurate identification of coccidioidomycosis is essential in reducing disease severity [22].

Clinical symptoms include fever, chills, pneumonia, persistent chest pain, cough, erythema nodosum, erythema multiforme, erythematous rash, maculopapular rash and arthritis [22]. Coccidioidomycosis initially manifests as an acute or chronic pulmonary infection and can progress to extrapulmonary infection of bone, skin, organs or the central nervous system. A detailed clinical description of pulmonary and extrapulmonary dissemination of coccidioidomycosis are discussed below. It should be noted that coccidioidomycosis, either

isolated to the respiratory tract or extrapulmonary infection contributes a health burden on both the patient's quality of life and the health care system. Patients on average miss 14 days of school or work and if hospitalized, treatment and hospital stay can be expensive and prolonged [22].

Pulmonary coccidioidomycosis

The clinical course of pulmonary coccidioidomycosis can present as either an acute or chronic respiratory infection. While the majority of patients may be asymptomatic, some patients present with a variety of symptoms. Chough, chest pain, night sweats and fever are common clinical symptoms seen in cases of pulmonary coccidioidomycosis and it can be difficult to distinguish from community acquired pneumonia (CAP) due to bacterial infection, [23]. In Arizona, primary coccidioidal pneumonia is a common cause of CAP [23]. Symptoms of acute infection usually occur 1 to 3 weeks after inhalation of coccidioidal arthrocondia and is usually self-limiting. Acute pulmonary coccidioidomycosis typically resolves within weeks to months without treatment [23]. Chronic pulmonary coccidioidomycosis can occur months to years after an acute infection [24]. Rare sequela seen in chronic pulmonary coccididoidomycosis, are residual pulmonary nodules, bronchopleural fistula and empyema [24]. Distinctive radiographic features seen in chest x-ray include, dense infiltrate, pleural effusions, associated hilar or mediastinal adenopathy. Additionally, cases can present with bilateral lung involvement [24-25].

Extrapulmonary coccidioidomycosis

Extrapulmonary coccidioidomycosis represents a serious clinical complication of this fungal disease and it can be fatal if not treated. Extrapulmonary or disseminated

coccidioidomycosis cases can range from less than 1% of all coccidioidomycosis cases to as high as 30% [9]. Dissemination has been shown to occur through hematogenous spread of *Coccidioides spp*. with the lungs being the primary source of disseminated infection [23]. The most common sites for extrapulmonary coccidioidomycosis is, skin, lymph nodes, bones/joints, and central nervous system [9].

Due to multiple extrapulmonary sites as potential targets for dissemination, numerous clinical symptoms are seen. Skin infections presents as a variety of lesions. These include, nodules, papules, pustules, furuncles, verrucous plaques, abscess, granulomatous lesions and ulcerations. Sites most commonly effected in coccidioidomycosis skin involvement are the head, neck and chest [26]. Bone and joint infections can result in arthritis and eventual bone destruction [9]. In skeletal coccidioidomycosis, about 40% of these cases have more than one bone infected with the vertebral bodies or pelvis being the most common sites of infection [9]. Additional sites for bone infection are the axial skeleton including vertebrae, skull, sternum and ribs [9]. Joint disease presents as synovitis with effusion. If dissemination occurs in the central nervous system, coccidioidal meningitis is the common clinical presentation [27]. Clinical symptoms of coccidioidal meningitis are, fever, headache, meningeal irritation and cognitive impairment [27]. Coccidioial meningitis has a high mortality rate, 70% in treated cases and 100% mortality in untreated cases [27].

Diagnosis

Patient's medical and travel history, clinical symptoms, physical examination and laboratory testing are integral to the diagnosis of coccidioidomycosis. Confirmatory diagnostic tests comprise either immune assays designed to detect antibodies against coccidiosis's antigens or identification of fungal spherules in tissue, sputum or other body fluids [28]. Serological

testing in suspected coccidioidomycosis patients is both prognostic, allowing for assessment of disease progression or resolution as well as diagnostics. Complement fixation (CF) test, immunodiffusion (ID) or enzyme-linked immunosorbent assay (EIA) test determine the presence of IgG or IgM specific C*occidoides ssp.* antibodies. A positive ID test is suggestive of a recent, recurrent or active infection while a positive CF test indicates a late or chronic disease status [28]. The commercially available EIA test for *Coccidioides spp.* antibodies have a sensitivity of 94.8% and a specificity of 98.5%. [28]. Upon a positive immunological based test, antibody titration is required. An antibody titer greater than or equal to 1:16 is considered active disease. A commercially available skin test, Spherulin™ is also available, however a positive skin test is an indication that the patient's cellular immunity is active. Research suggests that a patient with a positive skin test is at a reduced risk of coccidioidomycosis dissemination and that therefore, this test has more prognostic value than diagnostic value [29]. Additionally, a chest X-ray can be performed to evaluate *Coccidiodes ssp.* lung infection. For severe, disseminated cases where CNS involvement is suspected, a lumbar puncture is mandatory. Currently 23 states report confirmed cases of Coccidioides spp. infection to the National Notifiable Disease Surveillance System [30].

Vaccine Development

Currently no vaccine is available for coccidioidomycosis. However, researchers argue that a vaccine is feasible based on the natural human infection course that results in a lifelong immunity to *Coccidioides spp*. Moreover, it is estimated that a coccidioidomycosis vaccine would protect approximately 20 million people residing in endemic areas including over 350,000 military personal stationed in these regions [31]. Early vaccine studies used formalin killed spherule (FKS). These studies were conducted in mice and eventually tested in humans.

Although the animal studies showed protective immunity to *Coccidioides spp*., FKS failed to reach efficacy in the human phase 3 clinical trial [31]. A Heat kill yeast (HKY) vaccine derived from *Saccharomyces cerevisiae* showed promise as a pan-fungal vaccine. However, the degree of protection against *Coccidioides spp.* challenge in the mouse model of coccidioidomcyosis did not show superior protection compared to the FKS vaccine [32]. Continued research into the development of an efficacious coccidioidomycosis vaccine is ongoing.

Treatment

Antifungal agents available to treat coccoidal infections are the azole agents (fluconazole, itraconazole, voriconazole) and either the deoxycholate or lipid-based preparations of amphotericin B are recommended for sever or refractory cases [33].

Treatment modalities range from observation to antifungal prophylaxis depending on the severity of disease and presence of known risk factors discussed below. Observation with supportive measures such as respiratory physical therapy is recommended for patients with mild or no debilitating symptoms and are not immunosuppressed [28]. For patients that present with significantly debilitating illness, antifungal treatment is recommended [34] Additionally, antifungal treatment should be started in patients hospitalized due to coccidioidal symptoms or symptoms related to other comorbidities attributed to the infection. [28]. Clinical practice guidelines recommend that extrapulmonary soft tissue coccidioidomycosis be treated with oral azoles [28]. In the most severe clinical manifestation of coccidioidomycosis, coccidioidal meningitis lifelong oral azoles are an option of auxiliary therapy [28].

Risk factors for severe and disseminated disease

Geographical exposure whether through travel to or residence in areas of the Southwestern United States and southern regions of Mexico and South America are a principle risk factor for coccidioidomycosis [9]. Severe and disseminated disease is higher in people with suppressed immune systems. [9]. These include people taking immunosuppressive medication such as corticosteroids and TNF-alpha inhibitors [34]. Solid organ transplant recipients who reside in endemic areas and require lifelong cell-mediated immune suppression are at a higher risk for severe and disseminated disease [34]. Reported rates for disseminated coccidioidomycosis and associated mortality are as high as 72% within this population [9]. Gender and race have shown to be important risk factors for disseminated disease with men at greater risk than women and those with Filipino decent having the highest disseminated coccidioidomycosis risk [21]. African Americans are also at an increased risk for sever or disseminated disease [21]. The underlying etiology for this racial preference is not known however early research suggests that the ABO blood group as well as the HLA types may play a role in the pathophysiology of this fungal infection [35]. The very young and those with advanced age have a higher risk of chronic pulmonary infection and disseminated disease [24].

Additional risk factors related to occupation, military activity and incarceration within endemic areas have been associated with coccidioidomycosis [36-37]. Epidemiological investigation among a group of solar power farm construction workers located in endemic regions of California showed a higher rate of clinical coccidioidomycosis for workers who reported frequent exposure to dust clouds or storm conditions at the work site [36]. Cluster outbreaks of coccidioidomycosis within military institutions have been reported [38]. A report published in 2004 showed an increase in disseminated coccidioidomycosis cases at a US military hospital located within the endemic area compared to previous years [38]. Additionally, an

increase in coccidioidomycosis among inmates of correctional facility located within an endemic area have been reported [39].

Manuscript introduction

Coccidioidomycosis is a fungal respiratory disease caused by the inhalation of *Coccidioides* species spores that are most frequently found in areas where the soil is dry and alkaline, including the southwestern United States, parts of Mexico and Central and South America. [1-2]. The CDC estimates that approximately 150,000 infections are attributed to coccidioidomycosis in the United States annually [40]. The majority of infections are asymptomatic with symptomatic infections presenting as flu like illness that is self-limiting. An estimated 3-5% of symptomatic coccidioidomycosis infections disseminate and one third of these cases are fatal [41]. Additionally, in a small proportion of coccidioidomycosis patients, illness is prolonged and often times requires lifelong treatment [41]. Recently, concern has grown over a reported increase in the risk of exposure to *Coccidoides spp*. spores for populations in endemic areas, specifically military personnel, inmate populations, and solar panel workers [42].

Coccidioidomycosis represents a substantial healthcare burden within endemic states. The annual incidence of coccidioidomycosis within the United States increased from a rate of 5.3 per 100,000 in 1998 to a rate of 42.6 per 100,000 in 2011 [43-44]. Additionally, data from enhanced surveillance of coccidioidomycosis in Arizona indicated that total cost for hospitalizations due to coccidioidomycosis reached $86 million in 2007 [45]. Compounding the healthcare burden of coccidioidomycosis is the difficulty in diagnosing coccidioidomycosis which is commonly misdiagnosed for community-acquired pneumonia due to bacteria [23]. Misdiagnoses can contribute to an increase in the cost for care due to misuse of antibacterial

agents for this patient population [23]. Early diagnosis and initiation of antifungal therapy is important in preventing disease progression [46-47]. Furthermore, the rate of treatment relapse with the gold standard therapy, azoles antifungals, range from 16-67% at initial regimen costs ranging from 5,000-20,000$ per year [44].

While there are numerous studies examining risk factors for coccidioidomycosis, there are limited studies evaluating potential sociodemographic characteristics and comorbidities as factors associated with coccidioidomycosis hospitalization. Moreover, several of these studies utilized national administrative data sources which do not reflect the sociodemographic of the endemic populations [48]. Our study describes inpatient incidence of hospitalization for coccidioidomycosis and sociodemographic factors associated with this population using data from a large inpatient population. Additionally, we describe seasonal incidence for both California and Arizona. The results of our study will contribute to a better understanding of the factors related to coccidioidomycosis hospitalization compared to hospitalization for other causes. Moreover, our findings will aid healthcare providers in identifying potentially at-risk populations potentially leading to early diagnosis and treatment initiation.

Methods

We conducted a cross-sectional study to assess the sociodemographic and comorbidity factors associated with hospitalization due to coccidioidomycosis versus hospitalization for other causes in California and Arizona. Hospital discharge data obtained from the State Inpatient Dataset (SID) for both California and Arizona for years 2005-2011 were used in this study. The SID is part of the Healthcare Cost and Utilization Project (HCUP) developed by the Agency for Healthcare Research and Quality under The United States Department of Health and Human Services (HHS). HCUP consists of a collection of healthcare databases and software tools

collected by Federal and State institutions as well as private and public hospital organizations. The SID represents all-payer inpatient discharge information collected from nonfederal (e.g. not military, Veterans Administration or Indian Health Services), non-psychiatric and community hospitals. Private, public and university-affiliated medical centers are also included in the SID. The SID contains patient level data; however, personal identification information is not present in the SID and therefore it is not considered protected health information (PHI) and is excluded from Internal Review Board (IRB) review. Over 100 clinical and nonclinical variables are included in the SID [48]. Combining both California and Arizona SID for years 2005-2011 resulted in a cohort of over 33.0 million inpatients.

The study population includes all inpatient discharges for HCUP-defined hospitals from California and Arizona for year 2005-2011. A coccidioidomycosis case is defined as a primary and secondary diagnosis identified by the International Statistical Classification of Diseases and Related Health Problems version 9 (ICD-9) codes assigned for coccidioidomycosis. (Table 1). All patient discharges recorded in the SID for California and Arizona for years 2005-2011 were included in our study. The outpatient population was excluded from our study because information on outpatients is not collected in the SID. Population denominator data for the HCUP SID datasets consists of decennial census with annual estimates for years 2005-2007 and the American Community Survey for years 2007-2011. [49]

In order to assess potential cofactors of coccidioidomycosis hospitalization several sociodemographic and patient-level comorbidity factors were included in our analysis. Independent variables were chosen based on clinical and epidemiologic factors that were suggested in the medical literature to be associated with a higher rate of coccidioidomycosis infection or severe coccidioidomycosis infection. Additionally, we examined important

demographic factors that we believed may be important confounders. Our primary outcome is hospitalization due to coccidioidomycosis. The analysis examines several potential factors of coccidioidomycosis hospitalization. Sociodemographic factors include age, gender, race, patient location characterized by degree of urbanization, and household income. We hypothesized rural persons were at higher risk given lack of pavement, more contact with soil and potentially more exposure to the outdoor environment. Patient household income was included in our analyses to identify the presence of potential heath disparities within different socioeconomic groups for coccidioidomycosis hepatization. We hypothesized persons of lower socioeconomic status were at a higher risk attributed to financial barriers to healthcare and an overall lower health status compared to persons with higher socioeconomic status. To allow for assessment of potential age group related risk for coccidioidomycosis hospitalization the continuous variable Age was stratified into six categories, (0-17, 18-29, 30-39, 40-49, 50-59 & >60 years). The age stratification groups are similar to a previous study that also used an administrative level dataset. [3]. Race was categorized as Caucasian (non-Hispanic), African American (non-Hispanic), Hispanic, Native American or Alaska Native (non-Hispanic), Asian/Pacific Islander (non-Hispanic) and Other or multiple race (non-Hispanic). Urbanization is stratified into four rural-urban patient locations, urban (metropolitan), large rural town (micropolitan), small rural town and isolated small rural area. The stratification used by HCUP to generate the condensed Urbanization variable within the SID database is based on rural urban commuting areas (RUCA) and assignment into ZIP codes using population and commuting information from the 2000-year Census [50]. Household income is represented by the quartile of the median household income based on the patient's zip code and was included as a community level socio-economic factor. Hospital location state (California or Arizona) was also included as a variable in the analysis.

In order to examine associations between hospitalization for coccidioidomycosis and other underlying health factors, we included several comorbidity conditions. Comorbidity for AIDS, diabetes, obesity and chronic pulmonary disease were included in the analysis due to previous reports showing increased coccidoidomycosis frequencies within these patient populations [9] . Using the Clinical Classification Software (CCS) grouping system, ICD-9 diagnostics codes were grouped into 285 mutually exclusive and clinically meaningful categories [51]. Comorbidity for AIDS, diabetes, obesity and chronic pulmonary disease were included in the analysis. To adjust for overall inpatient comorbidity burden, the Elixhauser index is also included. The Elixhauser index has been shown to be a valid approach to control for individuals' overall burden of illness in studies that use administrative databases like ours. [48-52] The Elixhauser index was calculated using the Elixhauser Comorbidity Software, version 3.7. [51].

Environmental factors such as seasonal rainfall, earthquakes and soil disruptions have been shown to be associated with higher incidences of reported coccidioidomycosis cases [53-54]. We hypothesized that coccidioidomycosis cases would increase following an increase in rainfall. The incubation for coccidiodiomycosis is not well established, therefore we performed analysis for a one too three-month lag between higher rainfall and increased coccidiodomycosis infections. [9]. The average monthly rainfall was calculated using data obtained National Oceanic and Atmospheric Administration. [55] Due to monthly variability in rainfall between California and Arizona, analysis was done separately for each state. Spearman correlation was calculated using SAS software, [56]

To describe the characteristics of the study population, we report the distribution of the socioeconomic and comorbidity factors for cases and controls refer to Table 1. Categorical variables were defined by frequencies for each defined category. Bivariate analyses were

performed to determine whether the chosen socioeconomic and comorbidity factors are independent risk factors for coccidioidomycosis hospitalization. We calculated odds ratios comparing odds of hospitalization for coccidioiomycosis versus hospitalization for other conditions for each of our independent variables. Referent groups are consistent with previous research papers [57]. All factors with a *P* values of < 0.20 in the bivariate analysis were included in a multivariate logistic regression analysis. We calculated rates of hospitalization for coccidiomycosis by race and ethnicity for the years 2005-2011 using data from the 2010 US Census, assuming a stable population for our study time frame.

Multivariable logistic regression modeling was used to determine the magnitude to which sociodemographic factors and comorbidities during hospitalization were associated with the odds of having a coccidioidomycosis diagnosis. We report the unadjusted odds ratios with 95% confidence intervals as well as adjusted odds ratios using the final adjusted model determined through the model selection procedure. SAS® version 9.2 (SAS Institute Inc., Cary, North Carolina, 18) was used for all statistical analyses [56].

To assess multicollinearity among variables in our multivariable model , variance decomposition proportion (VDPs) analysis was performed using the SAS macro Collin [58]. Variables with VDPs greater than 30 indicate a collinearity problem and would be excluded from our model, however, no VDPs greater than 30 were present in our assessment for multicollinearity.

Results

A total of 33,645,973 patients were hospitalized in Arizona and California between the years 2005-2011.. Among these hospitalized patients, a total of 23,758 hospitalizations due to

coccidioidomycosis occurred. The most common coccidioidomycosis diagnoses for both states was "primary coccidioidomycosis". The subsequent frequencies of coccidioidomycosis diagnoses which included primary cutaneous coccidioidomycosis, coccidioidal meningitis, progressive coccidioidal and chronic and unspecified pulmonary coccidioidomycosis, varied by state. Arizona had an over six-fold higher coccidioidomycosis hospitalization incidence rate compared to California over the study time frame, 198.9/per 100,000 vs 29.6/per 100,000 person years. (Table 2). The following sections present findings regarding our three-main analyses: annual rates by race and ethnicity in California and Arizona; average monthly rates by levels of precipitation in California and Arizona; and factors associated with odds of hospitalization for coccidioidomycosis versus other causes during the periods of 2005-2011.

Annual incidence rates per 100,000 persons for coccidioidomycosis-associated hospitalizations were determined for different racial groups and years included in this study (Figure 1). Consistent with previous research that reported higher incidence of coccidioidomycosis associated hospitalization for Asian/Pacific Islanders and African Americans compared to other racial groups [20], in our analysis Asian/Pacific Islanders and African Americans had the highest incidence rates across all years in addition to the calculated average annual incidence (Figure 1). The average annual incidence of coccidioidomycosis associated hospitalization per 100,000 persons for Asian/Pacific Islanders and African Americans was 11.8/1000,000 persons (95% CI 9.1-14.4) and 12.8/100,000 persons (95% CI 10.9-14.6) respectively. For all other races the average annual incidence was Caucasians 6.2/100,000 persons(95% CI 5.2-7.2), Native American 5.6/100,000 persons (95% CI 4.2-7.1), Hispanic 5.2/100,000 persons (95% CI 4.3-6.1) and other 0.5/100,000 persons (95% CI 4.1-7.1).

To evaluate whether seasonal rainfall, a climate-related condition, has an impact on the monthly incidence of hospitalization due to coccidoidomycosis, monthly cases and precipitation totals were determined.

In Arizona, monthly hospitalizations associated with coccidioidomycosis showed high-incidence periods during the winter months of October, November and December. The average precipitation for these months ranged from 0.6-0.84 inches. Additionally, both September and February showed the lowest incidence of hospitalizations. In Arizona, peak precipitation occurred in August and March (Figure 2). The spearman correlation coefficient for no lag time and all three lag time frames were not statistically significant and therefore no correlation between seasonal rainfall and hospitalized cases due to coccidioidomycosis was found for hospitalizations due to coccidioidomycosis occurring in Arizona (Table 3).

In California, incidence of coccidioidomycosis associated hospitalizations peaked in October. Peak rainfall occurred during the later winter months, December, January and February 3.02, 3.6, and 3.1 inches respectively. A negative correlation was found between seasonal rainfall and hospitalized cases due to coccidioidomycosis for California. Spearman correlation coefficient for the one, two and three-month lag times were statistically significant at $\alpha = 0.05$. (Table 3).

The demographics and comorbidities of our study population are summarized in Table 4. Bivariate analysis of these factors associated with cocci included all factors that were independently associated with a patient's odds of hospitalization due to coccidioidomycosis relative to hospitalization for other reasons. Females were less likely than males to be hospitalized due to coccidioidomycosis (adjusted odds ratio (aOR 0.40 [95% CI 0.39-0.41]). Middle-aged patients were more likely to be hospitalized due to coccidioidomycosis than both

non-senior adults and children as well as younger adults; age 0-17 years: (aOR 0.17 [95% CI 0.16-0.18]); age 30-39 years: (aOR 1.42 [95% CI 1.35-1.50]); age 40-49 years; (aOR 1.50 [95% CI 1.43-1.59]; age 50-59; (aOR 1.07 [95% CI 1.02-1.30]). Senior adults age >60 years were less likely to be hospitalized due to coccidioidomycosis. Age >60;(aOR 0.51 [95% CI 0.49-0.54]). Multivariable analysis showed that African Americans had higher odds of hospitalization due to coccidioidomoycosis vs Caucasians patients, (aOR 1.98 [95% CI 1.89-2.06]). Hispanic, Native American/Alaska Native and Other category patients all had higher odds of hospitalization associative with coccidioidomycosis compared to Caucasians patients. Hispanic (aOR 1.32 [95% CI 1.27-1.36]), Native American/Alaska Native (aOR 1.26. [95% CI 1.18-1.35]). Asian/Pacific Islander and Other racial ethnic groups did not show significant difference in odds of hospitalization due to coccidioidomycosis compared with the Caucasian population, (aOR 0.903 [95% CI 0.81-1.01, 1.07]) and (aOR 1.07 [95% CI 0.94-1.22]) respectively.

Where a patient resided was scientifically associated with hospitalization due to coccidioidomycosis. Patients residing in a large rural area showed higher odds of hospitalization due to coccidioidomycosis compared to patients residing in an urban area. (aOR 2.28 [95% CI 2.19-2.39]). For those patients who resided in either a small rural town or an isolated rural area, the odds of hospitalization due to coccidioidomycosis compared to patients living in an urban area were decreased (aOR 0.93 [95% CI 0.85-1.01]) and (aOR 0.95 [95% CI 0.84-0.91)]) respectively. Patients who reported incomes in the first through third quartiles of income had a lower odds of hospitalization due to coccidioidomycosis compared to fourth quartile (wealthiest income) patients, first quartile (aOR 0.87 [95% CI 0.84-0.91]) second quartile (aOR 0.78 [95% CI 0.74-0.81]), third quartile (aOR 0.87 [95% CI 0.83-0.81]). Additionally, the state in which a patient was hospitalized in was associated with hospitalization due to coccidioidomycosis

compared to hospitalization due to other reasons. Patients residing in Arizona had higher odds of being hospitalized due to coccidioidomycosis than patients residing in California. (aOR 6.42 [95% CI 6.25-6.60]).

Several comorbidity where associated with hospitalization due to coccidioidomycosis. AIDS patients had reduced odds of hospitalization due to coccidioidomycosis [aOR 0.75 [95% CI 0.58-0.99]). Uncomplicated diabetes (aOR 1.47 [95% CI 1.41-1.52]) and chronic pulmonary disease (aOR 1.59 [95% CI 1.54-1.65]) showed an increase in the likelihood of hospitalization due to coccidioidomycosis. Obese patients were less likely to be hospitalized due to coccidioidomycosis compared to hospitalization for other causes. (aOR 0.78 [95% CI 0.74-0.83]).

Discussion

Using an administrative dataset obtained from the Healthcare Cost and Utilization Project, we conducted a cross-sectional study to identify sociodemographic predictors for hospitalization due to coccidioidomycosis vs hospitalization due to other causes. In addition, we examined several comorbidity measures to determine whether or not they are associated with coccidioidomycosis hospitalization relative to other-cause hospitalization. Furthermore, we determine overall incidence of hospitalization due to coccidioidomycosis during the study time period as well as evaluate whether environmental changes influenced the frequency of coccidioidomycosis hospitalizations. To the best of our knowledge, this is the first study to evaluate sociodemographic and comorbidity predictors of hospitalizations associated with coccidioidomycosis using a large inpatient population-based dataset.

Independently, the sociodemographic predictors such as gender, age, race/ethnicity, and place of residence all showed a statistically significant association with hospitalizations due to coccidioidomycosis. These results are consistent with previously identified sociodemographic risk factors for coccidioidomycosis determined from previous epidemiological studies [52]. Of note, our results for the independent risk assessment of patient household income showed that patients who reported household income fitting into to the lower quartiles of income (First-Third quartile) stratification had a lower odd for hospitalization related to coccidioidomycosis versus higher income patients (Fourth quartile). This finding surprised us and may be attributed to economic issues hindering access to health care or due to more common use of hospitals for conditions that higher income populations might handle with primary care providers. In our multivariable model, African Americans where at a higher risk of hospitalization due to coccidioidomycosis compared to Caucasian populations. Using a California inpatient dataset, Sondermeyer et al showed an increased relative risk for hospitalization within this race/ethnic population, consistent with our findings [59]. Based on these findings, we did a post-hoc analysis to examine whether there was an interaction between African Americans living in rural areas and that interaction's association with coccidioidmycosis hospitalization. We found this population was at a 35% increase in odds of hospitalization due to coccidioidomycisis (aOR 1.35 [95% CI 0.89-2.06]) although this relationship was not statistically significant.

Hospitalized patients in Arizona were at a much higher risk for hospitalization due to coccidioidomycosis than patients residing in California. A study published in 2016 detailing the distribution of coccidioidomycosis cases reported that Arizona accounted for 66% of cases while California accounted for 31% [60]. Arizona has been reported to be one of the fastest-growing states in the United States [60-61]. This expansion is the result of increased immigration of

persons from non-endemic areas who subsequently may be susceptible to coccidioidomycoses infections [61]. Occupational coccidioidomycosis represents a significant public health concern within endemic areas with construction workers and agricultural works at a higher risk for infection compared to other occupational categories [62-63]. Additionally, outbreaks have occurred within military populations who train in coccidioidomycosis endemic areas [31].

Another important finding was the identification of several comorbidities that were associated with an increased likelihood of hospitalization due to coccidioidomycosis. These include uncomplicated diabetes and chronic pulmonary disease. In support of our findings, a prior epidemiological study showed diabetes to be a contributing cause of death in coccicdioidmycosis patients, suggesting diabetes may be associated with more severe coccidioidomycosis infection and hence higher risk of hospitalization [64]. In our multivariable model, obese patients were at reduced risk of hospitalizations due to coccidioidomycosis vs non-obese patients which was an unexpected and novel finding. Additionally, when controlling for other co-variates, our analysis determined that patients with AIDS were at a lower risk for coccidioidomycosis vs patients without AIDS. A study coinciding with the time frame of this study published by Masannat and Ampel suggests a decrease in the incidence and severity of coccidoidomycosis within the HIV-1 infected population may be attributed to the introduction of potent Antiretroviral therapy (ART). [65]. In our bivariate analysis of the Elixhauser index, higher comorbidities as indicated by a higher index source, were associated with an increased odds for hospitalization due to coccidioidomycosis (aOR=1.02 [95% CI 1.02-1.03]) for each point in the Elixhauser score). Several studies designed to characterize coccidioidomycosis-associated death have included several comorbid conditions in their multivariable model, but this is the first study to our knowledge to include all 29 comorbid conidiations present in the

Elixhauser comorbidity index score. Although this study did not exclusively look at fungal meningitis, a recent study published by Charalambous et al, showed that a common characteristic of fungal meningitis due to either crypto, coccidioidomycosis, histoplamosis or candidaiias is the presence of comorbid conditions. This study showed that 60% of patients diagnosed with fungal meningitis had a Charlson Comorbidity Index, score of greater than 3 [44].

There were several limitations in this study. Including patients with a secondary diagnosis code for coccidioidomycosis could results in an overestimation for the incidence of disease due to diagnostic coding error. However, our study followed previously reported methods for epidemiological study inclusion criteria [59]. Administrative databases are prone to missing data and selection bias maybe introduced when large amounts of missing data are present. However, investigation has several strengths. First, this is the first study to examine the association between hospitalization due to coccidioidomycosis and comorbidity measures including the recently available Elixhauser index. Secondly, to our knowledge, our study is novel in that it utilized a large population-based cohort consisting of hospitalized patients from two highly endemic areas, Arizona and California where prior studies used both inpatient or outpatient cohorts from individual endemic states.

In conclusion, we found multiple sociodemographic predictors and comorbidities associated with hospitalizations due to coccidioidomycosis in an inpatient dataset consisting of individual level data obtained from the State Inpatient Dataset for Arizona and California. Disseminated coccidioidomycosis represents a disease with a high mortality rate and therefore early identification of populations at highest risk may be helpful for limiting disease-associated morbidity and mortality. Our findings may allow for the targeting of certain groups of high-risk individuals for prevention measures and early coccidioidomycosis screening within the hospital

setting. Additionally, our study describes potential high-utilizers of healthcare services. Hospitalized coccidioidomycosis patients require costly disease management, with reports estimate around $55,000 per hospital visit for this patient population [59]. These results contribute to a better understanding of the inpatient coccidioidomycosis population. Studies like ours bring attention to healthcare provides of the potential disease burden attributed to coccidioidomycosis. A greater understanding of coccidioidomycosis is essential, as a survey of healthcare providers in Arizona reveled that greater than 50% of healthcare provides lacked integral knowledge regarding the disease which included the recent IDSA treatment guidelines [28]. Future research should be directed toward development of early diagnosis and treatment modalities especially in high-risk patients. Continued vaccine development would also aide in reducing the health and finical burden attributed to coccidioidomycosis hospitalization [31].

Expanded Discussion

The Healthcare Cost and Utilization Project (HCUP), with its numerous databases and analytical tools, represents a vital Healthcare information resource. Using these databases, researchers from various healthcare backgrounds have been able to ask a wide range of research questions. These questions range from inpatient costs analysis for different diseases, measurements of quality of care and assessment of factors that may be driving hospital readmissions. The Center for Medicare and Medicaid Services (CMS) reports the U.S. health expenditures published in The National Health Expenditure Accounts (NHEA). The recent 2016 national health expenditures reached 3.3 trillion dollars with 32% allocated to Hospital care [66]. Hospital care represents the category with the highest percentage of allocated health dollars followed by both physician and clinical services and other spending services coming in second at 20% health dollar allocation [66]. Epidemiological studies using inpatient databases like the

National Inpatient database (NID) or the State Inpatient Database (SID) collected by HCUP are warranted to better understand healthcare expenditures and to characterize the populations who are utilizing them.

In the present study we asses epidemiological, sociodemographic and comorbidity factors associated with patients hospitalized for Coccidioidomycosis compared to hospitalization due to other causes using the SID for both California and Arizona, years 2005-2011. Hospitalized coccidioidomycosis cases contribute significantly to both the overall impatient healthcare cost through longer hospital stays and expensive interventions and the health burden experienced by patients in missed work time [44,48]. There are numerous studies focused on coccidioidomycosis however, to our knowledge our study is the first to use a combined cohort consisting of inpatient health information dataset from two endemic areas.

Our analysis identified sociodemographic factors associated with hospitalization due to coccidioidomycosis compared to hospitalization due to other causes. Among hospitalized patients, coccidioidomycosis is more likely to be found among African Americans, likely due to their increases risk of sever disseminated infection [9]. It is well documented that the African American population experiences health disparities [67-68]. For example, the diagnosis rate of HIV is substantially higher for the African American population compared to the overall diagnostic rate of the United States, 49.4/per 100,000 population and 13.8/per 100,000 population respectively [69]. Cancer and stroke are two additional diseases disproportionately affecting the African American population [68]. Numerous health equality programs designed to eliminate or reduce health disparities have been initiated within the United States such as the Healthy People 2020 program and The National Partnership for Action to End Health Disparities [70-71]. Our findings suggest that a health disparity exists for African Americans in relation to

hospitalization due to coccidioidomycosis compared to hospitalization due to other causes. Therefore, health equality initiatives designed to reduce disparities should consider including coccidioidomycosis.

In the presented study, analysis of comorbidities reveled that both diabetes mellitus (DM) and chronic pulmonary disease were risk factors for hospitalization due to coccidioidomycosis (Table 2). Furthermore, the combined comorbidity score, the Elixhouser score, showed that higher comorbidities was associated with an increased odds for hospitalization due to coccidioidmycicsis (aOR=1.02[95% CI 1.02-1.03]) for each point in the total Elixhausre score. The presence of comorbidities can contribute to a worse health outcome [72]. Identification of the comorbidities that have an influence on selected health outcomes would benefit patient care.

Diabetes mellitus represents a major public health issue. It is the 7th leading cause of death in the United States [73]. Current estimates show that 9.4% of the US population has diabetes mellitus [73]. This is an increase from the previous estimates, prior to 2017, that reported a prevalence of 7.2% [73]. Diabetes contributes to an overall decrease in health status. For example, diabetes mellitus increases the risk of heart attack by 1.8 times [73]. Additionally, diabetics are at a higher risk of kidney failure, lower limb amputations and adult onset blindness [73]. Diabetes mellitus patients are also at a higher risk for greater severity of some infectious diseases including coccidoiodmycsossis [74]. Santelii et al, showed that diabetes mellitus patients were less likely to resolve their cccidioidal infection compared to non-diabetic patients [74]. Contributing to the health burden experienced by diabetes mellitus patients, our study showed that persons with diabetes were at a higher risk for hospitalization due to coccidioidomycosis compared to hospitalization due to other causes.

One of the goals proposed in the Healthy people 2020 initiative is to reduce the disease burden of diabetes mellitus [71]. Our findings may contribute to reducing the infectious disease health burden experienced by diabetes mellitus patients within a hospital setting by increasing healthcare providers awareness of the risk of coccidioidomycosis infection for this population.

In addition to diabetes mellitus, our study identified chronic pulmonary disease as a comorbidity that was associated with an increase in hospitalization associated with coccidioidomycosis [Table 4]. Coccidioidomycosis infection occurs thorough inhalation of coccidiodies spores [9]. Complications can arise if the organisms are not cleared from the lungs. These complications include, extrapulmonary dissemination to vital organs or skin. Dissemination to the central nervous system is the most severe manifestation of coccidioidomysois and if often times fatal [75]. In a study published by Ampel et al, among 8 patients who were initially treated with antifungal therapy but developed complications, four had chronic lung disease as an underlying disease [76].

The Elixhauser comorbidity index consists of a group of 30 comorbidity indicators [51]. We incorporated the Elixhauser score in our multivariable model to reduce bias by controlling for baseline characteristics between groups. The results of our multivariable model show that comorbidities was associated with an increased odds for hospitalization due coccidiomycosis (aOR=1.02]95% CI 1.02-1.03]0 for each point in the total Elixhauser score. To our knowledge, ours is the first study to include the Elixhauser score within a multivariable model designed to identify factors of hospitalization due to coccidioidomycosis compared to hospitalization du to other causes.

Resent surveillance data on coccidioidomycosis show increasing infections within endemic areas [77]. For example, Charalambous et al. show that fungal meningitis due to

Coccidioidomycosis has increased 6.0% from year 2000 to 2012 [77] . Elucidating the epidemiological mechanism involved in this increase is currently under study. It has been suggested that one contributing factor is an increase in occupational exposure, specifically, exposure related to solar energy development and increased migration of susceptible hosts [33].

Taken together our study contributes to a better understanding of the sociodemographic and comorbidly features of hospitalizations due to coccidioidomycosis compared to hospitalization due to other causes. With increasing incidence of coccidioidomycosis infections, studies like ours will enhance healthcare providers awareness of populations at higher risk.

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Table 1: Demographic features and comorbidities for hospitalized patients (SID CA & AZ,2005- 2011)

	N (%)	
Total	23758 (0.1)	33622215 (99.9)
Characteristic	Cocci (case)	Control
Sex		
Female	8687 (37.1)	19080000 (58.6)
Male	14735 (62.9)	14735 (41.4)
Age (years)		
0-17	1025 (4.3)	6729194 (20.0)
18-29	2888 (12.2)	4125162 (12.5)
30-39	3566 (15.1)	3441015 (10.4)
40-49	4544 (19.2)	3184698 (9.6)
50-59	4393 (18.6)	3712402 (11.2)
>60	7251 (30.6)	1210317 (36.3)
Race/ethnicity		
White	12047 (54.5)	1810474 (54.3)
African American	2681 (12.1)	2266488 (7.3)
Hispanic	5792 (26.2)	9041211 (29.2)
Native American/Alaska Native	905 (4.1)	2040092 (6.6)
Asian/Pacific Islander	425 (1.9)	213243 (0.7)
Other	254 (1.2)	594988 (1.9)
Rural-Urban Patient Location		
Urban	17985 (84.2)	30966060 (92.1)
Large rural town	2539 (11.9)	1601255 (5.0)
Small rural town	595 (2.8)	634359 (2.0)
Isolated rural	222 (1.1)	290338 (0.9)
Household Income		
First quartile	6777 (30.4)	9074550 (28.0)
Second quartile	5486 (24.6)	8335102 (25.7)
Third quartile	5341 (24.0)	8068555 (25.0)

	Fourth quartile	4668 (21.0)	6927733 (21.3)
Mortality			
	Died in Hospital	589 (2.5)	639629 (1.9)
	Alive at discharge	23147 (97.5)	327283392 (98.1)
State			
	CA	10970 (46.3)	21196962 (63.3)
	AZ	12700 (53.7)	12449011 (36.7)
Comorbidity			
	AIDS		
	Yes	60 (0.3)	56682 (0.2)
	No	23698 (99.7)	33589291 (99.8)
	Diabetes (uncomplecated)		
	Yes	4678 (19.7)	4097289 (12.3)
	No	19080 (80.3)	292586682 (87.7)
	Obeseity		
	Yes	1620 (6.8)	2380693 (7.1)
	No	22138 (93.2)	309935037 (92.9)
	Chronic pulmonary disease		
	Yes	4922 (20.7)	4141441 (12.4)
	No	18836 (79.3)	292253060 (87.6)

Table 2: Incidence of hospitalization for Coccidioidomycosis: California and Arizona SID, 2005-2011

		N (rate/100,000)	
Variable	N (%)	CA	AZ
Hosptializations			
All	23758 (100)	11043 (29.6)	12715 (198.9)
Diagnosis (ICD-9 Code)			
Primary coccidioidomycosis (114.0)		6107 (16.4)	7812 (122.2)
Primary cutanious and NOS (114.1 & 114.9)		553 (1.5)	693 (10.8)
Coccidioidal meningittis (114.2)		1316 (3.5)	983 (15.4)
Progressisive coccidioidal NEC (114.3)		1855 (5.0)	1455 (3.9)
Chronic and unspecified pulmonary (114.4 &114.5)		1295 (3.5)	1863 (29.1)

California Census 2010, 37,253,956

Arizona Census 2010, 6,392,017

Table 3. Seasonal Precipitation and coccidioidomycosis hospitalization for California and Arizona

State	Lag Time	Spearman Correlation Coeff.	P-value
California	No Lag	-0.032	0.77
	1 Month Lag	-0.28	0.01
	2 Month Lag	-0.41	0.0001
	3 Month Lag	-0.42	0.0001
Arizona	No Lag	-0.13	0.24
	1 Month Lag	-0.2	0.07
	2 Month Lag	-0.18	0.11
	3 Month Lag	0.1	0.38

Table 4: Predictors of Coccidioidomycosis Hospitalization (SID CA & AZ, 2005- 2011)

Total	3.34E+07	3.34E+07
Characteristic	OR (95%) CL	aOR (95%) CL
Sex		
Female	0.41 (0.40-0.43)	0.40 (0.39-0.41)
Male	Ref.	Ref.
Age (years)		
0-17	0.22 (0.21- 0.24)	0.17 (0.16-0.18)
18-29	Ref.	Ref.
30-39	1.48 (1.41-1.56)	1.42 (1.35-1.50)
40-49	1.92 (1.83-2.01)	1.50 (1.43-1.59)
50-59	1.7 (1.61-1.77)	1.07 (1.02-1.3)
>60	0.86 (0.83-0.90)	0.51 (0.49-0.54)
Race/ethnicity		
White	Ref.	Ref.
African American	1.66 (1.59-1.73)	1.98 (1.89-2.06)
Hispanic	0.90 (0.87-0.93)	1.32 (1.27-1.36)
Native American/Alaska Native	0.62 (0.58-0.67)	1.26 (1.18-1.35)
Asian/Pacific Islander	2.8 (2.54-3.01)	0.903 (0.81-1.01)
Other	0.60 (0.53-0.68)	1.07 (0.94-1.22)
Rural-Urban Patient Location		
Urban	Ref.	Ref.
Large rural town	2.43 (2.33-2.53)	2.28 (2.19-2.39)
Small rural town	1.48 (1.36- 1.60)	0.93 (0.85-1.01)
Isolated rural	1.16 (1.02,-1.33)	0.95 (0.84-0.91)
Household Income		
First quartile	1.09 (1.06, 1.13)	0.87 (0.84-0.91)
Second quartile	0.97 (0.93, 1.01)	0.78 (0.75-0.81)
Third quartile	0.98 (0.94, 1.02)	0.87 (0.83-0.81)
Fourth quartile	Ref.	Ref.
Mortality		

Died in Hospital	1.34 (1.24-1.45)	1.12 (1.03-1.22)
Alive at discharge	Ref.	Ref.
Elixhauser Index		
Score	1.03 (1.03-1.03)	1.02 (1.02-1.03)
State		
CA	Ref.	Ref.
AZ	5.9 (5.74-6.01)	6.42 (6.25-6.60)
Comorbidity		
AIDS		
Yes	1.5 (1.16-1.90)	0.75 (0.58-0.99)
No	Ref.	Ref.
Diabetes (uncomplecated)		
Yes	1.75 (1.7-1.80)	1.47 (1.41-1.52)
No	Ref.	Ref.
Obeseity		
Yes	0.95 (0.90-1.00)	0.78 (0.74-0.83)
No	Ref.	
Chronic pulmonary disease		
Yes	1.84 (1.79-1.9)	1.59 (1.54-1.65)
No	Ref.	Ref.
Interaction		
Black & Rual		
Yes	3.45 (2.37-5.03)	1.35 (0.89-2.06)
No	Ref.	Ref.

Figure 1. Annual incidence rates Per 100,000 persons by racial and ethnic groups.

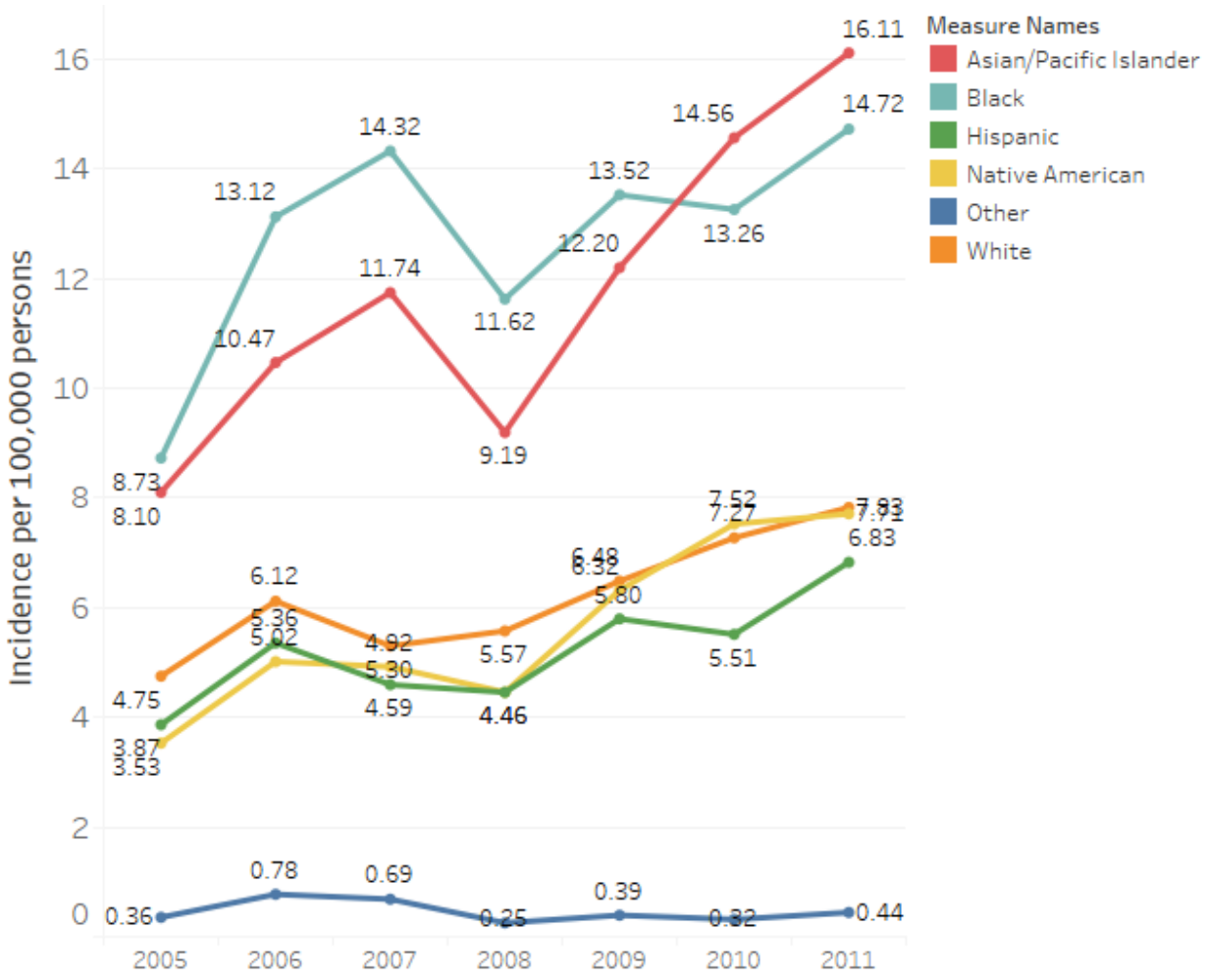

Figure 2. Monthly Hospitalization for Arizona and California with average seasonal precipitation amounts.