66TH ANNUAL COCCIDIOIDOMYCOSIS STUDY GROUP MEETING

ORAL PRESENTATION ABSTRACTS

COCCIDIOIDOMYCOSIS CLUSTER AMONG WILDLAND FIREFIGHTERS, CALIFORNIA 2021

Dorothy Maffei[1,2], Marisa Donnelly[1,3], Gail Sondermeyer Cooksey[1], Barbara Materna[1]
[1]California Department of Public Health, Richmond, USA. [2]Council of State and Territorial Epidemiologists, Atlanta, USA. [3]Centers for Disease Control and Prevention, Atlanta, USA

INTRODUCTION: In July 2021, the California Department of Forestry and Fire protection (CAL FIRE) notified the California Department of Public Health (CDPH) of seven wildland firefighters from the same fire crew who developed respiratory symptoms concerning for coccidioidomycosis. CDPH and CAL FIRE began an investigation to identify and confirm cases and better understand coccidioidomycosis risk among these wildland firefighters.

METHODS: CDPH reviewed medical records and conducted standardized phone interviews with the three firefighters with confirmed coccidioidomycosis.

RESULTS: Illness onset dates and work history suggested exposure to Coccidioides likely occurred while working on a fire in late June 2021 in the California Central Valley. All interviewed patients reported heavy dust exposure, two disclosed having heard of Valley fever before being tested for it, none reported wearing respiratory protection, and all were hospitalized. CAL FIRE was proactive about recommending coccidioidomycosis testing following possible exposure, and cases were diagnosed within 12 days as compared to a median of 55 days from onset to diagnosis reported generally for coccidioidomycosis.

CONCLUSION: As coccidioidomycosis and wildfire frequency increase in California, additional exposure prevention tools, increased awareness, and early recognition and disease management are needed to protect wildland firefighters.

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CONTRIBUTION OF BIOLOGIC RESPONSE MODIFIERS TO THE RISK OF COCCIDIOIDOMYCOSIS SEVERITY

Fariba Donovan[1,2], Ferris Ramadan[3], James Lim[2], Julia Buchfuhrer[2], Rebia Khan[4], Natalie DeQuillfeldt[2], Natalie Davis[2], Ashwini Kaveti[2], Melanie De Shadarevian[5], Edward Bedrick[3], John Galgiani[1,2]
[1]Valley Fever Center for Excellence, University of Arizona, Tucson, AZ, USA. [2]Department of Medicine, University of Arizona, Tucson, AZ, USA. [3]Department of Epidemiology and Biostatistics, University of Arizona, Tucson, AZ, USA. [4]Department of Medicine, University of Arizona, Phoenix, AZ, USA. [5]A. T. Still University, School of Osteopathic Medicine, Mesa, AZ, USA

INTRODUCTION: The risk of coccidioidomycosis (CM) as a life-threatening respiratory illness or disseminated CM (DCM) increases as much as 150-fold in immunosuppressed patients. The safety of biologic response modifiers (BRMs) as treatment for patients with autoimmune disease (AI) in CM-endemic regions is not well defined. We sought to determine that risk in the Tucson and Phoenix areas.

METHODS: We conducted a retrospective study reviewing demographics, Arizona residency length, clinical presentations, specific AI diagnoses, CM test results, and BRM treatments in electronic medical records of patients ≥18 years old with International Classification of Diseases (ICD-10) codes for CM and AI from 1 October 2017 to 31 December 2019.

RESULTS: We reviewed 944 charts with overlapping ICD-10 codes for CM and AI, of which 138 were confirmed to have both diagnoses. Male sex was associated with more CM ($P = .003$), and patients with African ancestry were 3 times more likely than those with European ancestry to develop DCM ($P < .001$). Comparing CM+/AI+ ($n = 138$) with CM+/AI– ($n = 449$) patients, there were no significant differences in CM clinical presentations. Patients receiving BRMs had 2.4 times more DCM compared to pulmonary CM (PCM).

CONCLUSIONS: AI does not increase the risk of any specific CM clinical presentation, and BRM treatment of most AI patients does not lead to severe CM. However, BRMs significantly increase the risk of DCM, and prospective studies are needed to identify the immunogenetic subset that permits BRM-associated DCM.

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HEALTH DISPARITIES IN COCCIDIOIDOMYCOSIS INCIDENCE — CALIFORNIA, 2000–2019

Marisa Donnelly[1,2], Gail Sondermeyer Cooksey[1], Alyssa Nguyen[1], Adam Readhead[1], Alexander Yu[1], Duc Vugia[1], Seema Jain[1]
[1]California Department of Public Health, Richmond, CA, USA. [2]Centers for Disease Control and Prevention, Epidemic Intelligence Service, Atlanta, USA

Background: Coccidioidomycosis is a fungal infection caused by soil-dwelling Coccidioides immitis or posadasii, which people can contract by inhaling spores from the environment. Although most infected persons recover without symptoms or with mild illness, ~1% of patients develop severe disseminated disease that can result in death. In California, incidence rates are highest among persons aged 40–59 years and people who self-identify as Black or Hispanic or Latino. We sought to estimate association between coccidioidomycosis incidence rates and California's Healthy Places Index (HPI), a metric of community health, to guide public health practice and messaging toward less advantaged populations in California.

Methods: We analyzed California coccidioidomycosis cases reported during 2000–2019. Patients' residential addresses were geocoded, linked to data from the 2010 census, and categorized into 4 HPI quartiles based on census tract HPI score. Tracts in the lowest scoring HPI quartile (HPI 1) are less advantaged as measured by 25 health equity variables. For each HPI quartile, we calculated age-adjusted incidence by sex, age, and race. Multivariable negative binomial regression was used to calculate incident rate ratios and assess trends.

Results: In total, 74,622 coccidioidomycosis cases were reported in California during 2000–2019; incidence rate/100,000 population was highest among people aged 40–59 years (11/100,000 population), males (10.6/100,000 population), and persons aged 20–39 years (9.3/100,000 population). Overall, incidence was highest in HPI 1 and decreased with increasing HPI scores (incidence rate ratio HPI 1 vs HPI 4 = 7.03, P <0.001). When stratifying by HPI, the highest incidence rate was for persons aged 40–59 years in HPI 1 (21.7/100,000 population).

Conclusions: In California, coccidioidomycosis incidence rates were highest in less advantaged communities. Socially and culturally appropriate guidance for coccidioidomycosis outreach programs, testing, and treatment should be strengthened for these communities.

WORK-RELATED COCCIDIOIDOMYCOSIS IN CALIFORNIA: EXAMINING THE BURDEN OF DISEASE USING WORKERS' COMPENSATION AND ARCHIVAL DATA

Savannah Hunter
UC Davis Sociology, Davis, USA

INTRODUCTION: Coccidioidomycosis is a health hazard for workers in endemic areas; however, systematic analysis of work-related disease has been challenging due to limitations in available data.

METHODS: I examine the potential burden of work-related coccidioidomycosis using two data sources. First, I analyze 2240 claims submitted to California's Workers Compensation Information System (WCIS) for coccidioidomycosis from 2000 to 2019 using R Studio. This work was supported by a collaboration with the California Department of Public Health – Occupational Health Branch and the California Department of Industrial Relations – Division of Workers Compensation. I obtained IRB approval for working with confidential WCIS data. I calculated the number of claims by employers' industry, worker occupation, sex, and age at time of injury. I produced preliminary disease incidence rates for 5-year periods using data from the American Community Survey. WCIS data can only capture disease among workers who submitted a claim to workers' compensation. To complement the analysis, I systematically collected data from state agency investigations and reports, news media, and legal cases and built an archival database of over 100 work-related exposures and outbreaks in California.

RESULTS: The WCIS data and the archival data point to similar findings. First, in line with broader disease surveillance, reports of work-related disease have increased. Incidence rates from the WCIS data have doubled from .39 out of 100,000 workers between 2000-2004 to a high of .83 between 2015-2019. Second, the top three Census industries reporting work-related disease include Public Administration (44%), Construction (14%), and Agriculture (9%). Third, the most common Census occupations included Protective Service Occupations (28%), Construction and Extraction Occupations (18%), and Healthcare Practitioners and Technical Occupations (9%). Fourth, most work-related disease is reported by men (82%). However, reports from women (65%) outnumber claims from men in healthcare occupations and analysis of injury descriptions suggests that 73% of laboratory-based exposures occurred among women.

CONCLUSION: This research provides both an up-to-date and systematic analysis of work-related coccidioidomycosis in California and suggests future directions for work-related disease prevention efforts.

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REACTIVATION OF COCCIDIOIDAL DISEASE PROGRESSION IN ASYMPTOMATIC, STABLY INFECTED MICE

Lisa Shubitz[1], Daniel Powell[1,2], Christine Butkiewicz[1], Hilary Moale[1], Hien Trinh[1], Jeffrey Frelinger[1], John Galgiani[1]
[1]Valley Fever Center for Excellence, University of Arizona, Tucson, USA. [2]Department of Immunobiology, University of Arizona, Tucson, USA

Introduction: Reactivation of coccidioidomycosis in humans is reported under conditions of severe immunosuppression, such as AIDS and solid organ transplantation. In a new model of chronic, stable infection in mice, dexamethasone suppression was applied in a pilot study of the loss of infection control.

Methods: B6D2F1 mice were infected IN with 50 spores of the less virulent *C. posadasii* strain 1038 (Cp1038) and rested for 5 weeks. On day 37 p.i., dexamethasone (DXM) was added to the drinking water at a rate of 6 mg/L. Control mice received plain water. Mice (2 per time point and treatment) were sacrificed on days 0, 5, 10, 15 and 20 for histopathology (left lung) and flow cytometry (right lung). For flow cytometry, granulomas in the right lung were dissected closely with a 3 mm skin biopsy punch and placed in RPMI. Left lungs were fixed in 4% paraformaldehyde for 24 hrs and moved to 70% ethanol. Multiparameter flow cytometry assessed total cell counts in granulomas, viability, and myeloid and lymphoid cells and subsets. Five micrometer sections of the left lung were stained routinely with H&E.

Results: Histopathology of baseline and untreated mice revealed well-organized granulomas with a necrotic center, a fibrogranulomatous mantle region, and lymphoid aggregates on the borders of the mantle. Spherules were estimated at 0-1 per 400X field and were all located within the borders of the necrotic center. By day 5, neutrophil populations were diminished in mice receiving DXM and there was an increase in spherules as well as observation of them outside the previous borders of the necrotic center. Lymphoid aggregates were still observed. By day 15, there was a decrease in all immune cell types and the lesions ceased to have any organization. Lymphoid aggregates were not present, replaced by sheets of plasma cells. On day 20, large numbers of neutrophils had returned to the mixed inflammatory lesion, fibrosis was not observed, and spherule numbers were >20 per 400X field, dispersed throughout the lesion. Flow cytometry revealed that by day 5 in treated mice, there was a 1-1.5 log reduction in total cells and in T cells, B cells, and neutrophils. Neutrophils rebounded robustly by day 20 while T-cell numbers remained depressed.

Conclusion: This observational study demonstrates that there are rapid changes in spherule numbers and cell populations in the previously controlled granulomas when immunosuppressive doses of DXM are administered to mice. This shows that reactivation can be modeled in mice and suggests a plethora of cellular and molecular studies to understand the host pathogen relationship in controlled and reactivated coccidioidomycosis.

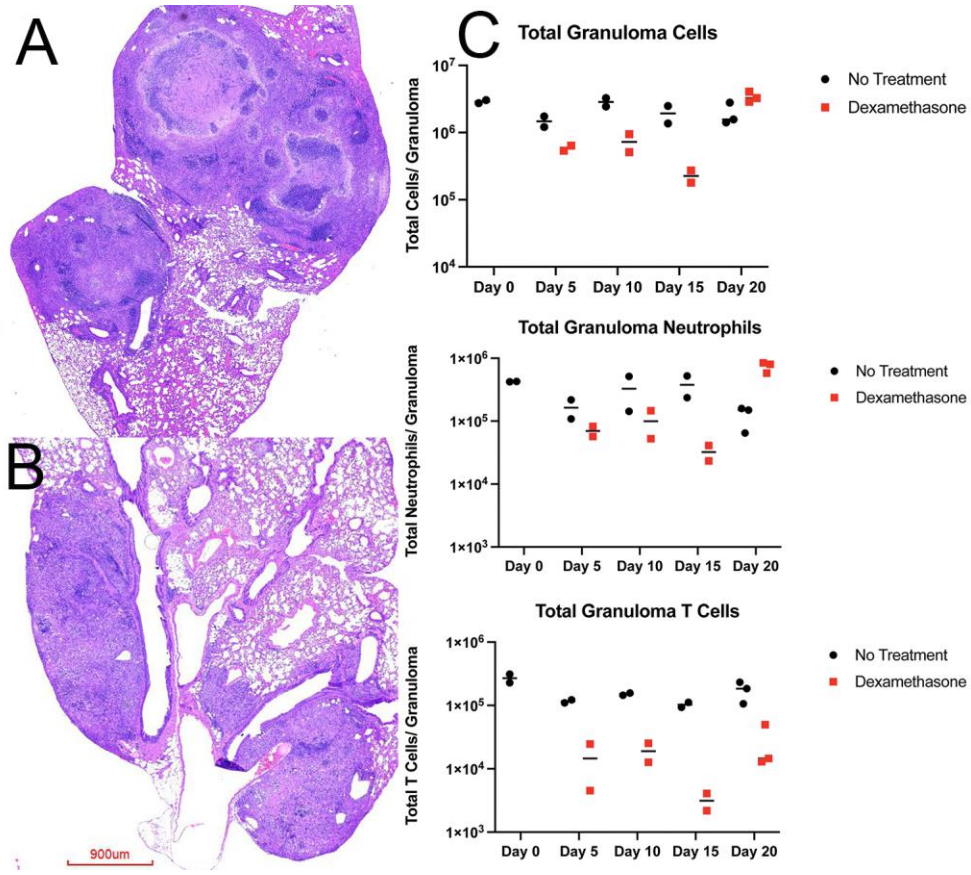

Figure: A) Normal granulomas in untreated B6D2F1 mouse. Necrotic center contains neutrophils and spherules with a thick fibrogranulomatous mantle and lymphoid aggregates on the borders of the mantle. **B)** B6D2F1 mouse after 20 days DXM administration. There are few lymphocytes, and the neutrophils have recovered but there is total loss of granuloma structure; **C)** Total cell numbers in the granulomas decrease >1 log by day 15 and rebound by day 20. T-cell populations reduce and do not recover; the cell increase is due to neutrophils. (A and B, H&E stain, magnification 1.3x and 1.4x, respectively; C, Vicell - granuloma viable cell counts, flow cytometry - T-cell ($CD3^+$) and neutrophil ($CD11B^+$, $Gr\text{-}1^+$) counts)

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COCCIDIOIDOMYCOSIS SCORE SYSTEM: MSG 2.0

Royce Johnson[1,2,3], Rupam Sharma[1,2], Valerie Civelli[1], Vishal Narang[1], Rasha Kuran[1,2,4], Carlos D'Assumpcao[1,2,3], Arash Heidari[1,2,3]
[1]Kern Medical, Bakersfield, USA. [2]Valley Fever Institute, Kern Medical, Bakersfield, USA. [3]David Geffen School of Medicine, UCLA, Los Angeles, USA. [4]David Geffen School of Medicine, UCLA, Bakersfield, USA

Introduction: In 1981 the Mycoses Study Group (MSG) developed a scoring system to quantify severity of fungal infections. The score system was modified for coccidioidal infection treatment trials with azole drugs. The Valley Fever Institute has endeavored to develop a score system specifically for coccidioidomycosis that is less subjective than the original. The intent was to develop a score system that was more specifically applicable to the great variety of coccidioidal illness: pulmonary, disseminated, meningeal. It is important to measure the patients' perception of health to assess benefit of health care interventions. We included the PRO/QOL as a choice of questionnaires to establish patient perceptions of changes in their health and satisfaction.

Methods: We evaluated the original scoring system and multiple studies that used this in the evaluation of Coccidioidomycosis. Variables that are difficult to measure are eliminated. Variables that were easily reproduced were added.

Results: Included in the revised non-meningeal scoring system are weight loss, eosinophilia, markers of inflammation, skin tests, imaging, and coccidioidal serology. There is a separate section for pulmonary disease with newly included physiologic scoring for severity. Specific sections for skin, subcutaneous abscess, joints, bone, intraabdominal, lymph nodes, and other new disseminated sites are included.

The revisions to the MSG scoring system for meningeal disease are simplified and objectified. The evaluation of mental status is modernized. A new section for increased intracranial pressure is added to include this critical advance in knowledge about initial and subsequent patient care.

Conclusions: The goal of this effort is to update the 1981 MSG scoring system by incorporating newer understanding of coccidioidal disease into the numerical standardized format. We are endeavoring to improve usability, reliability and pertinence of outcome measurement of any anti coccidioidal therapy. Future validation studies are planned. The addition of validated patient related outcomes measures adds a new dimension to evaluating therapeutic interventions.

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AN OUTBREAK OF COCCIDIOIDOMYCOSIS AMONG GEOLOGY STUDENTS

Julia Wang[1], Rupam Sharma[2,3], Arash Heidari[2,3,4], Royce Johnson[2,3,4]
[1]Cal Tech, Pasadena, USA. [2]Kern Medical, Bakersfield, USA. [3]Valley Fever Institute, Kern Medical, Bakersfield, USA. [4]David Geffen School of Medicine, UCLA, Los Angeles, USA

Introduction: The fungal arthroconidia Coccidioides species are known to be endemic in the soil of multiple areas in the Southwest dessert United States, most commonly San Joaquin Valley of California. In October of 2021, a group of geology graduate students traveled to multiple locations in the Carrizo Plains located at southeastern San Luis Obispo County to map and study the local geology. The group was unaware of the potential for substantial exposure to Coccidioides in the area evaluated. No specific remediation was taken to prevent the accusation of airborne arthroconidia. It is interesting to note, this outbreak engrafted during the peak time of the SARS-CoV-2 pandemic. The purpose of this report is to extend knowledge of the epidemiology of Coccidioides in southwest California.

Methods: This study was approved by the Caltech Institutional Review Board. A retrospective chart review was performed on all 12 patients using electronic health records. A literature search was conducted on PubMed and google scholar using the following search terms: valley fever, coccidioidomycosis.

Results: In Fall 2021, a group of 12 Caltech individuals traveled to multiple locations in the Carrizo Plains to map and study the local geology. The first identified case occurred when a student was admitted to the hospital for progressive respiratory symptoms and a rash. A diagnosis of coccidioidomycosis (CM) was made by a consulting infectious disease specialist. A second student was also hospitalized around the same time for “nonspecific” viral symptoms which was also eventuated in the diagnosis of pulmonary CM. A third student presented to Caltech student wellness (CSW) services for prolonged respiratory symptoms with the onset of three weeks upon returning from the trip. One week following the trip the professor also developed progressive protracted respiratory symptoms and was seen at an outside facility and diagnosed with CM. This pattern of exposure was identified by the physician at CSW who then coordinated evaluation, diagnosis, and care for all 12 members of the group. Definitive immunoassay tests were performed by the UC Davis Coccidioidomycosis Serology Laboratory, resulting in a final confirmation of 5/12 positives, 4 of whom required treatment.

Conclusions: There are many unknown areas adjacent to San Joaquin Valley of California that are endemic to Coccidioides such as Southeastern San Luis Obispo County. This report should serve as a warning to individuals that participate in outdoor activities such as hikers, campers, geologists and construction workers to be wary of the potential risk of exposure to Coccidioides. The clinicians also should be aware of newly found endemic areas and have a low threshold to test for identification of Coccidioides.

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IMMUNOGENETICS ASSOCIATED WITH SEVERE COCCIDIOIDOMYCOSIS

Amy Hsu[1,2], Agnieszka Korzeniowska[1], Cynthia Aguilar[1], Jingwen Gu[1], Eric Karlins[1], Andrew Oler[1], Gang Chen[3], Glennys Reynoso[1], Joie Davis[1], Alexandria Chaput[4], Tao Peng[4], Ling Sun[3], Justin Lack[1], Derek Bays[5], Ethan Stewart[5], Sarah Waldman[5], Daniel Powell[4], Fariba Donovan[4], Jigar Desai[1], Nima Pouladi[4], Debra Long Priel[6], Daisuke Yamanaka[1], Sergio Rosenzweig[7], Julie Niemela[7], Jennifer Stoddard[7], Alexandra Freeman[1], Christa Zerbe[1], Douglas Kuhns[6], Yves Lussier[4], Kenneth Olivier[8], Richard Boucher[3], Heather Hickman[1], Jeffrey Frelinger[4], Joshua Fierer[9], Lisa Shubitz[4], Thomas Leto[1], George Thompson III[5], John Galgiani[4], Michail Lionakis[1], Steven Holland[1]
[1]NIAID/NIH, Bethesda, USA. [2]University of Maryland, College Park, USA. [3]University of North Carolina, Chapel Hill, USA. [4]University of Arizona, Tucson, USA. [5]University of California Davis, Davis, USA. [6]Leidos Biomedical Research, Inc., Frederick National Laboratory for Cancer Research,, Frederick, USA. [7]Department of Laboratory Medicine, CC, NIH, Bethesda, USA. [8]NHLBI/NIH, Bethesda, USA. [9]University of California San Diego, La Jolla, USA

Introduction: Disseminated coccidioidomycosis (DCM) is caused by Coccidioides, pathogenic fungi endemic to Western United States and Mexico. Illness occurs in approximately 30% of those infected, <1% of whom develop disseminated disease.

Methods: We enrolled DCM patients, performed whole-exome sequencing and assessed cytokine production in stimulated peripheral blood mononuclear cells (PBMC). Confocal microscopy co-localized DECTIN-1 and fungal endospores. Transfection demonstrated DECTIN-1, PLCG2, DUOX1 and DUOXA1 roles in b-glucan-stimulated H2O2 production. RNA was sequenced from STAT3-mutated, autosomal-dominant Hyper-IgE syndrome patients (AD-HIES) respiratory tissues. Duox1-/- mice were infected with Coccidioides.

Results: In an exploratory set of 67 DCM patients, two had haploinsufficient STAT3 mutations. Defects in b-glucan sensing and response were seen in 34/67 (50.7%) cases. Damaging CLEC7A (n=14) and PLCG2 (n=11) variants were found and PBMC from patients with these variants produced less b-glucan-stimulated TNF-a than healthy controls ($P<0.005$). Using ancestry matched controls, damaging variants in CLEC7A and PLCG2 were over-represented in DCM ($P=0.0206$, $P=0.015$, respectively) including CLEC7A Y238* ($P=0.0105$) and PLCG2 R268W ($P=0.0025$). In a validation cohort of 112 DCM patients PLCG2 R268W ($P=0.0276$), CLEC7A I223S ($P=0.044$), and CLEC7A Y238* ($P=0.0656$) were confirmed. Fifteen discovery cohort patients had heterozygous DUOX1 or DUOXA1 variants which impaired H2O2 production in transfected cells. AD-HIES patient airway epithelial cells had decreased DUOX1 and DUOXA1 transcripts. Duox1-/- mice had increased morbidity and mortality following Coccidioides infection.

Conclusions: Patients with DCM have impaired b-glucan sensing or response affecting H2O2 production. Genetically impaired Coccidioides recognition and cellular response decrease inflammatory cytokine production and are associated with disseminated coccidioidomycosis.

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INTEGRATING PUBLIC HEALTH SURVEILLANCE AND ENVIRONMENTAL DATA TO MODEL THE PRESENCE OF COCCIDIOIDOMYCOSIS.

Kimberly Kaufeld[1], Morgan Gorris[1], Andrew Greene[2], David Kline[3], Staci Hepler[2]
[1]Los Alamos National Laboratory, Los Alamos, USA. [2]Wake Forest University, Winston-Salem, USA. [3]Wake Forest School of Medicine, Winston-Salem, USA

INTRODUCTION: Due to regional differences in public health surveillance and under detection of infections, it is challenging to use reported coccidioidomycosis case data to characterize true disease risk. However, statistical modeling methods can help fill in this information, including in areas that do not have mandated reporting.

METHODS: Using monthly, county-level coccidioidomycosis case data and various environmental and socioeconomic characteristics, we use a binary model that estimates the unobserved presence of *Coccidioides*, while accounting for imperfect detection of coccidioidomycosis cases in Arizona, California, Nevada, New Mexico, and Utah from 2000-2015.

RESULTS: We estimate the presence of *Coccidioides* was associated with higher temperatures and soil moisture levels. Using these statistical relationships, we are able to map the county-level estimates of coccidioidomycosis case burden across the southwestern United States, providing a better understanding of the endemic areas and the presence of Coccidioides.

CONCLUSION: This work aims to help inform future surveillance needs and clinical awareness for coccidioidomycosis. Additionally, this approach can estimate the probability of presence of coccidioidomycosis in places that don't report.

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COCCIDIOIDES DETECTED IN RODENT BURROW SOILS, BUT UNDETECTED IN AGRICULTURAL SOILS OR SETTLED DUST, IN THE SAN JOAQUIN VALLEY IN CALIFORNIA

Robert Wagner[1], Liliam Montoya[1], Cheng Gao[2], Justin Remais[1], John Taylor[1]
[1]University of California Berkeley, Berkeley, USA. [2]Chinese Academy of Sciences, Beijing, China

Introduction: The reported incidence of coccidioidomycosis in the United States has increased by approximately six hundred percent over the past twenty years. Much is known about the geographic distribution of coccidioidomycosis cases, though comparatively little is known about the causative organism, *Coccidioides*, as to how it exists in the natural environment. A better understanding of the environmental biology of *Coccidioides*, particularly its seasonal dynamics, would aid in disease prevention and mitigation strategies.

Methods: Here, nearly one thousand soil and settled dust samples from the San Joaquin Valley in California were collected over the course of multiple years, and the presence of *Coccidioides* was determined using the CocciEnv qPCR assay. Additionally, the composition of the fungal community was determined using ITS metabarcoding. Approximately half of the samples were from four agricultural sites (surface soils, soil cores and settled dust) spanning 160km from Bakersfield, California to just south of Fresno, California. The remaining samples were from five undeveloped sites (rodent burrow soils and settled dust) on an 80km north-south transect along California highway 33.

Results: *Coccidioides* was detected in approximately one third of rodent burrow soil samples, with positive samples collected from all five undeveloped sites. *Coccidioides* was not positively detected in any soil samples from the four agricultural sites investigated and was undetected in all settled dust samples regardless of site. Where *Coccidioides* was positively detected, detection was strongly associated with the site where samples were collected, though unassociated with the month of collection. Detection of *Coccidioides* was not strongly correlated with the β-diversity (community structure) of the greater fungal community in the soils sampled. The two undeveloped sites with the highest *Coccidioides* detection rate were adjacent to substantial washes, whereas the remaining 3 undeveloped sites were not.

Conclusion: There is a high likelihood of finding *Coccidioides* in rodent burrows along California highway 33. It is possible that rodent burrows are the primary source of *Coccidioides* spores in the area around California highway 33, as the *Coccidioides* detection rate here far exceeds that of soils in general. *Coccidioides* was not positively detected in soils from the four agricultural sites studied here, suggesting that it is unlikely that *Coccidioides* would be found in soils on other agricultural fields in the San Joaquin Valley. The strong differences in the probability of detecting *Coccidioides* between individual highway 33 sites, and the lack of an association between *Coccidioides* detection and sampling month, indicate that spatial variables may be more important for predicting *Coccidioides* presence than temporal variables. It is not clear why *Coccidioides* was undetected in settled dust, especially at undeveloped sites along highway 33 where *Coccidioides* is prevalent in rodent burrow soils.

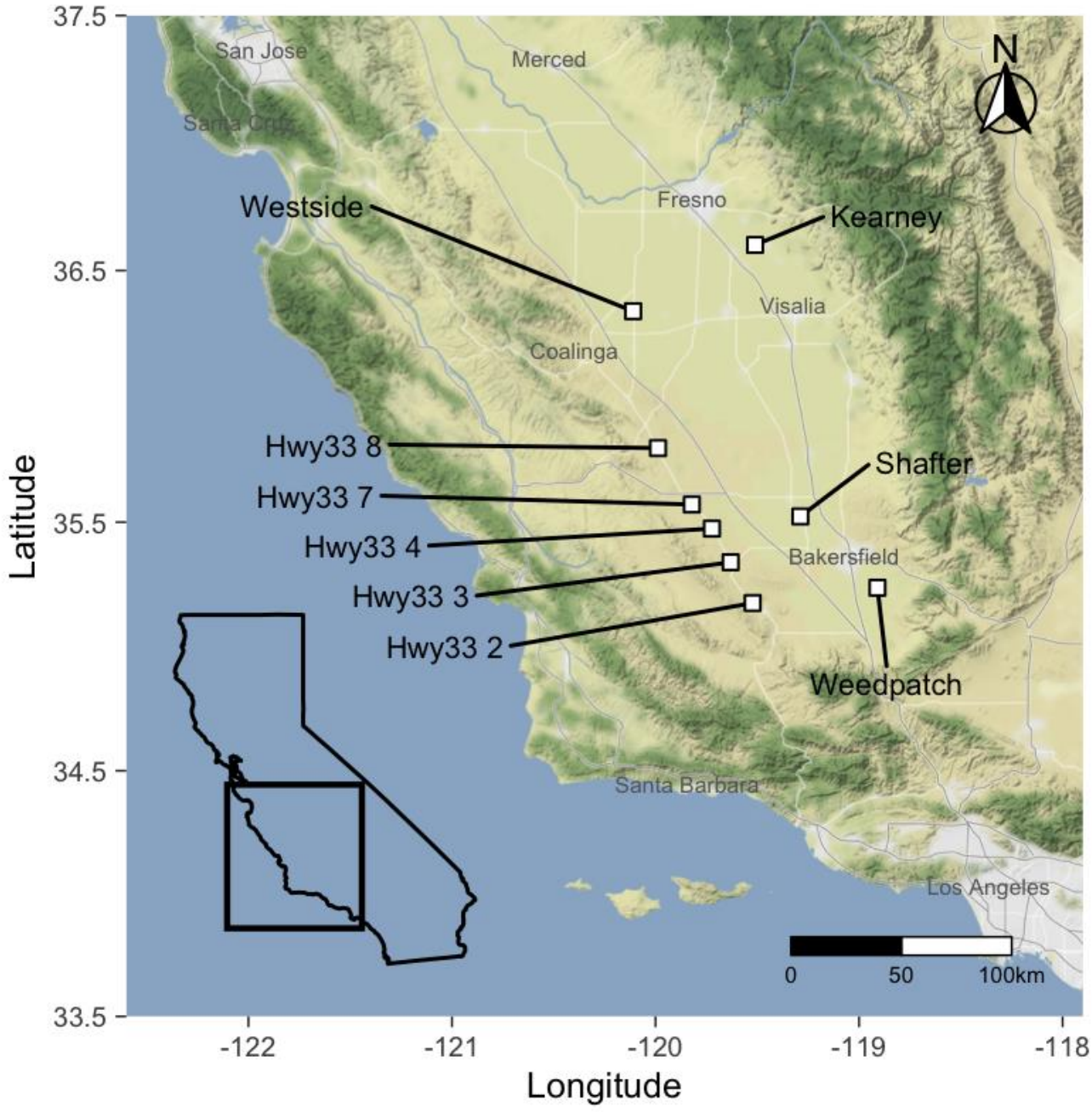

Figure 1: Map of soil collection locations

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RISK FACTORS FOR FLUCONAZOLE FAILURE IN THE TREATMENT OF COCCIDIOIDAL MENINGITIS

Simran Gupta, Neil M. Ampel, Marie F. Grill, Molly Klanderman, Janis E. Blair
Mayo Clinic, Phoenix, USA

INTRODUCTION: Azole therapy is the current standard of treatment for coccidioidal meningitis (CM). Guidelines from the Infectious Disease Society of America (IDSA) recommend oral fluconazole at a dose of 400 to 1200 mg daily as initial therapy. However, many patients fail therapy with fluconazole and require alternate agents for treatment. Robust data regarding treatment are lacking. We aim to understand risk factors for fluconazole failure.

METHODS: We conducted a single-center retrospective chart review of patients from our institution with CM, and identified patients using an electronic search of International Classification of Disease (ICD) versions 9 and 10, using codes 114.2, B38.4, and B38.9. We included patients with biochemical evidence of meningitis and positive serology, antigen, polymerase chain reaction or culture in the cerebrospinal fluid (CSF). We excluded patients without adequate treatment details, suspected but not laboratory-confirmed coccidioidal meningitis, and those who were not initiated on fluconazole as the first line of treatment. We defined fluconazole failure as any sustained increase in meningitis-related symptoms or progression of CSF or imaging abnormalities, with resultant medication change (either increase in fluconazole dosage or change to another medication for reasons other than fluconazole adverse effects or drug toxicity). This study was approved by the Mayo Clinic Institutional Review Board. Descriptive statistics were used for data analysis. Chi squared goodness of fit test was used for categorical variables and Analysis of Variance (ANOVA) was used for continuous variables.

RESULTS: From 1/1/99 to 5/15/21 we identified 102 patients with CM, and excluded 31 based on exclusion criteria, yielding 71 patients studied. Among the 71, 22 (31%) experienced fluconazole failure, requiring either increased dosage of fluconazole or alternate antifungal treatment. No statistically significant predictors of failure were found amongst the demographics, clinical characteristics, laboratory indices, and imaging findings between patients who failed fluconazole and those who did not. Patients who were previously treated for non-CNS coccidioidomycosis (N=19) had a higher rate of fluconazole failure (40.9% vs 20.4%), though the difference was not statistically significant ($p = 0.07$). Initial dosage of fluconazole was not found to be a statistically significant predictor of fluconazole failure (400 mg failure rate 7/17[41.2%] versus 800 mg failure rate 13/44[29.5%], $p = 0.39$). The median time to fluconazole failure was 7.7 months (range 2.0-25.5); the median time to failure was longer for patients with a prior diagnosis of non-CNS coccidioidomycosis (22.8 vs 6.5 months, $p=0.25$). There was insufficient data to compare time to failure by fluconazole dosing.

CONCLUSION: One-third of CM patients at our institution who were initiated on therapy with fluconazole failed treatment. Our study did not find any statistically significant predictors of failure, including initial dosage of fluconazole. A larger study may have detected a small difference. A randomized control trial would be ideal to further evaluate CM outcomes and ascertain risk factors for failure and most appropriate fluconazole dose for therapy.

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QUANTITATIVE BIOMARKERS TO DETERMINE RISK OF DISSEMINATED COCCIDIOIDOMYCOSIS

Sergio Barberan-Soler[1], Christian Ortiz[1], Deanna Fedash[1], Bianca Torres[2,3], Evan Lanuza[2,3], Royce Johnson[2,3,4]
[1]RealSeq Biosciences, Santa Cruz, USA. [2]Department of Medicine, Division of Infectious Diseases, Kern Medical, Bakersfield, USA. [3]Valley Fever Institute, Bakersfield, USA. [4]Department of Medicine, David Geffen School of Medicine UCLA, Los Angeles, USA

Introduction: Coccidioidomycosis is probably the endemic mycosis of most clinical importance. Multiple modalities have been established as diagnostic. This includes culture and histopathology. More recently, antigen testing and polymerase chain reaction have found limited applicability. The mainstay of diagnostics for almost 100 years has been serology for IgG and IgM antibodies. There are multiple modalities for measuring these antibodies. There is major variation between the results of this test in terms of sensitivity and specificity. Most of these tests lack sensitivity in early disease and do not define successful treatment with clarity. Therefore raison d'être for new test technology. This report explores a pilot study of coccidioidal RNA measurement as in early and more sensitive diagnostic.

Methods: Kern Medical has developed a biobank of specimens from the great diversity of patients with Coccidioidomycosis. The biobank was approved by the Kern Medical IRB. Thereby, patients were consented for use of their biologic specimens. 12 patients were selected from the biobank, 5 with disseminated disease and 7 with disease clinically limited to the lung at time of specimen collection. Circulating RNA was extracted from serum samples with a KingFisher (ThermoFisher), circulating RNA was profiled with RealSeq® proprietary technology. This technology takes advantage of novel developments to detect circulating RNAs from host and pathogens with high accuracy. Samples were sequenced with Illumina sequencers and data was analyzed using RealSeq's proprietary RiboMarker® bioinformatics pipeline.

Results: All disseminated cases had measurable coccidioidal specific RNA, two patients with primary disease had measurable coccidioidal specific RNA, and five patients with primary disease had undetectable coccidioidal specific RNA.

Conclusion: Coccidioidal RNA analysis shows promise as a diagnostic test with broad applicability. It is possible that it could serve as an early diagnostic test with increased sensitivity, and it conceivably could be developed to the holy grail of cocci testing - a test of control cure.

MODELING THE DISCHARGE OF INFECTIOUS ARTHROCONIDIA OF THE FUNGAL PATHOGEN *COCCIDIOIDES POSADASII* GROWING IN SOIL

Daniel Kollath, Bridget Barker
The Pathogen and Microbiome Institute at Northern Arizona University, Flagstaff, USA

INTRODUCTION: The inhalation of airborne infectious arthroconidia from the fungal pathogen *Coccidioidies posadasii* initiates the disease coccidioidomycosis (Valley fever). Being the only method of infection, the process of conidia discharge is essential to understanding the disease dynamics of Valley fever. Our aim was to quantify the amount of arthroconidia being discharged from soil over time and to study the effects that moisture and precipitation have on this biological process

METHODS: Soil was inoculated with the pathogen and grown under varying temperature and moisture conditions. Arthroconidia was trapped on a filter and quantified weekly with a hemocytometer. We fit a logistic growth curve model to estimate and predict discharge of each condition through time. This model is used to test hypotheses of peak temporal discharge of conidia.

RESULTS: The analysis shows that under all environmental conditions there is a logistic discharge pattern of arthroconidia that peak 4 weeks after inoculation followed by a plateau. Low moisture leads to a significant decrease in conidia production, although a high abundance is still produced under low moisture conditions. Arthroconidia are consistently being discharged into the ambient air despite no significant soil disruption.

CONCLUSION: The purpose of this study was to temporally quantify the production of infectious arthroconidia and to predict conditions that stimulate an increase in abundance in the environment that can lead to a surge in infections. A better understanding of this process allows for more robust disease surveillance and improved knowledge of the biology and ecology of this organism.

EXPLORING CYCLES OF COCCIDIOIDOMYCOSIS USING PATTERNS OF RELATIVE INCIDENCE IN ENDEMIC COUNTIES IN THE UNITED STATES

Malavika Rajeev, Samantha Williams, Mohammed Khan, Mitsuru Toda, Ana Litvintseva, Nancy Chow
Centers for Disease Control and Prevention, Atlanta, USA

Introduction: Coccidioidomycosis incidence varies substantially by time and place within the western United States, and the contributing factors, including public health surveillance biases like changes in diagnostics and environmental influences, are poorly understood. It is especially challenging to disentangle spatiotemporal changes in incidence caused by environmental factors, such as weather or climate, from those caused by concurrent differences in surveillance across time and space. We used national surveillance data to explore cycles of coccidioidomycosis incidence at the county level, focusing on relative rather than absolute patterns in incidence to control for the effects of surveillance biases.

Methods: We used data on coccidioidomycosis cases reported through the Nationally Notifiable Diseases Surveillance System (NNDSS) in seven states between 1999–2019. We aggregated the data to monthly case counts at the county level and calculated incidence using annual intercensal population estimates from the U.S. Census Bureau. We first used a conservative Box-Pierce white noise test to exclude data from counties that were too sparse or noisy for robust analysis, and we also excluded any counties which had fewer than 200 cases over the whole period. For the remaining counties, we smoothed and de-trended the time series so that relative patterns of incidence could be explored. We used wavelet analyses to extract the significant interannual periods from each of the county time series, analyzed coherence between counties, and examined broader correlations between cycles of incidence across temporal and spatial lags using spline correlograms.

Results: Approximately 40 counties passed the initial filter for further analyses, primarily counties in California and Arizona with high case counts. The time period between consecutive peaks in incidence varied across counties, with a median of 19 months and a range of 12 – 28 months. The specific period lengths identified for each county were sensitive to how the time series were detrended, but consistently ranged from 1 – 2 years. When comparing between counties, relative changes in incidence (i.e., whether incidence was increasing, decreasing, or peaking relative to recent months) were correlated in time (at up to approximately a three-month lag) and space (i.e., for counties up to ~250 km away from each other).

Conclusion: We found that peaks in coccidioidomycosis incidence occurred every one to two years. The time between peaks was not consistent across counties, and in some cases changed across the time series. In the future, we plan to evaluate how covariates such as timing of precipitation and drought, soil humidity, and other spatiotemporal factors can predict the relative patterns in incidence and how they are correlated with each other across time and space.

66TH ANNUAL COCCIDIOIDOMYCOSIS STUDY GROUP MEETING

COCCIDIOIDOMYCOSIS IN THE VETERANS HEALTH ADMINISTRATION (VHA), 2010-2021

Cynthia Lucero-Obusan[1], Patricia Schirmer[1], Gina Oda[1], Mark Holodniy[1,2]
[1]U.S. Department of Veterans Affairs, Public Health Program Office, Palo Alto, USA. [2]Stanford University Division of Infectious Diseases & Geographic Medicine, Stanford, USA

Introduction: The incidence of coccidioidomycosis (CM) has increased in recent years, but there is little data about CM in Veterans. Herein, we describe the epidemiology of CM in VHA during 2010-2021.

Methods: CM-coded hospitalizations (including those with a COVID-19 diagnosis during the same hospitalization) and outpatient visits, as well as Coccidioides culture results were obtained from VHA's Praedico Public Health Surveillance System (1/1/2010-8/31/2021). Data extracted included patient demographics, location, diagnosis codes, encounter details and deaths during CM-coded hospitalizations.

Results: A total of 6,878 unique patients were identified. Of these, 42 were identified by culture result only and had no CM-coded encounters during this time period. Median age at first CM encounter was 64 years (range 18-99), and 93% (6,392) were male. Race was 69.5% White, 15.8% Black/African American, 1.3% American Indian/Alaska Native, 3.5% Asian or Pacific Islander, 1.1% Mixed Race, and 8.7% missing. 9.5% were of Hispanic/Latino ethnicity. Nearly 70% (4,779) resided in HHS Region 9 (AZ, CA, HI, NV and Pacific territories), with the top counties of residence being Maricopa, AZ (1,285), Pima, AZ (989), Los Angeles, CA (315), Pinal, AZ (290), and Kern, CA (201). For 3,034 recorded hospitalizations (1,926 unique individuals), median stay was 5 days, with 513 (17%) admitted to an intensive care and there were 135 deaths during a CM-coded hospitalization (4.4%). Approximately 9% of CM-coded hospitalizations from March 2020-August 2021 were also coded with COVID-19 and 18% of those patients died during their hospitalization. There were 41,840 CM outpatient visits recorded (5,901 unique individuals). Hospitalizations and outpatient visits for 2010-2020 increased during the period evaluated and ranged from 186-323 admissions and 2,751-5,003 outpatient visits annually.

Limitations: Case finding was based on diagnosis codes and/or culture results but did not include other testing modalities. Therefore, cases are not necessarily laboratory-confirmed and we may have missed other cases that were laboratory diagnoses only. Veterans that were evaluated or treated at non-VA locations may not have been captured. Additionally, we did not assess for exposures or environmental/occupational risk factors related to CM.

Conclusions: CM causes substantial morbidity and mortality in Veterans with cases occurring primarily in AZ and CA. The number of VHA encounters and hospitalizations for CM has increased in recent years. More study is needed to determine whether patients co-infected with CM and COVID-19 are at higher risk for severe disease.

66TH ANNUAL COCCIDIOIDOMYCOSIS STUDY GROUP MEETING

INFLUENCE OF METEOROLOGICAL FACTORS AND DROUGHT ON COCCIDIOIDOMYCOSIS INCIDENCE IN CALIFORNIA, 2000–2020

Jennifer Head[1], Gail Sondermeyer-Cooksey[2], Alexandra Heaney[1], Alexander Yu[2], Isabel Jones[1], Abinash Bhattachan[3], Simon Campo[1], Robert Wagner[1], Whitney Mgbara[1], Sophie Phillips[1], Nicole Keeney[1], John Taylor[1], Ellen Eisen[1], Dennis Lettenmaier[4], Alan Hubbard[1], Gregory Okin[4], Duc Vugia[2], Seema Jain[2], Justin Remais[1]
[1]UC Berkeley, Berkeley, USA. [2]California Department of Public Health, Richmond, USA. [3]California State University - East Bay, Hayward, USA. [4]UC Los Angeles, Los Angeles, USA

Background: Coccidioidomycosis is an emerging infection in the southwestern United States. We examined the effects of precipitation and temperature on the incidence of coccidioidomycosis in California during 2000-2020, and estimated incident cases attributable to the California droughts of 2007-09 and 2012-15.

Methods: We analyzed monthly California coccidioidomycosis surveillance data from 2000–2020 at the census tract-level using generalized additive models. Models included distributed lags of precipitation and temperature within each endemic county, pooled using fixed-effects meta-analysis. An ensemble prediction algorithm of incident cases per census tract was developed to estimate the impact of drought on expected cases.

Results: Across 14 counties examined, coccidioidomycosis was strongly suppressed during, and amplified following, the 2007-2009 and 2012-2015 droughts. An estimated excess of 1,358 and 2,461 drought-attributable cases were observed in California in the two years following the 2007-2009 and 2012-2015 droughts, respectively. These post-drought excess cases more than offset the drought-attributable declines of 1,126 and 2,192 cases, respectively, that occurred during the 2007-2009 and 2012-2015 droughts. Across counties, a temperature increase from the 25th to 75th percentile (interquartile range) in the summer was associated with a doubling of incidence in the following fall (incidence rate ratio (IRR): 2.02, 95% CI: 1.84, 2.22), and a one IQR increase in precipitation in the winter was associated with 1.45 (95% CI: 1.36, 1.55) times higher incidence in the fall. The effect of winter precipitation was stronger (interaction coefficient representing ratio of IRRs: 1.36, 95% CI: 1.25, 1.48) when preceded by two dry rather than average winters. Incidence in arid lower San Joaquin Valley counties was most sensitive to winter precipitation fluctuations, while incidence in wetter coastal counties was most sensitive to summer temperature fluctuations.

Conclusions: In California, wet winters along with hot summers, particularly those following previous dry years, increased risk of coccidioidomycosis in California. Drought conditions may suppress incidence, then amplify incidence in subsequent years. With anticipated increasing frequency of drought in California, continued expansion of incidence, particularly in wetter, coastal regions, is expected.

66TH ANNUAL COCCIDIOIDOMYCOSIS STUDY GROUP MEETING

ELUCIDATING THE INTERACTIONS BETWEEN MACROPHAGES AND *COCCIDIOIDES*

Jane Symington, Allison Cohen, Mark Voorhies, Anita Sil
UCSF, San Francisco, USA

Introduction: Coccidioidomycosis or Valley Fever is a fungal infection caused by *Coccidioides* spp. with a wide range of outcomes of infection, from asymptomatic infection to meningitis, yet the host and fungal factors that underlie these differences remain largely unknown. We are investigating the role of innate immune cells in the early host response to infection, specifically the role of macrophages and G-protein coupled receptor C3aR1 in host response to *Coccidioides* arthroconidia.

Methods: Bone marrow derived macrophages were isolated from wildtype (C57BL/6) or C3aR1-/- mice. *Coccidioides posadasii* Silveira arthroconidia were used in all experiments. Macrophage phagocytosis of arthroconidia was examined by confocal microscopy using a dual staining approach, incubating macrophages with FITC-labelled arthroconidia at a multiplicity of infection (MOI) of 1 (1 arthroconidia for every macrophage) and at each time point labeling extracellular arthroconidia with Calcofluor White. To evaluate the ability of arthroconidia to transition to spherules, the host parasitic form, in the presence of macrophages, we incubated arthroconidia with macrophages at MOI 0.1 (1 arthroconidia for every 10 macrophages) or MOI 1 and examined fungal morphology by light microscopy over 72hrs. RNAseq was performed on RNA isolated from macrophages infected with *Coccidioides* arthroconidia at MOI 1 or MOI 0.1 at multiple timepoints (1hr, 24hrs, and 48hrs). All experiments were conducted at 37C and 5% CO2.

Results: We show that by 1 hr of infection, half of all macrophages had intracellular arthroconidia, with phagocytosis occurring as quickly as 15 min. Interestingly, early phagocytosis is dependent on the host complement 3a receptor (C3aR1), which our laboratory has shown is necessary for efficient phagocytosis of fungi by macrophages (https://www.biorxiv.org/content/10.1101/2021.12.30.474615v1). In macrophages lacking C3aR1, 10% of macrophages had phagocytosed arthroconidia compared to 45% in wildtype cells at 30 min. We next observed that the presence of macrophages strongly promoted the ability of arthroconidia to transition to spherules at temperatures that would not normally promote significant spherulation in vitro. Small spherules were observed within macrophages, in addition to larger extracellular spherules. Preliminary RNAseq data showed minimal changes in transcription at 1hr, with significant upregulation of macrophage genes associated with acute inflammation at 24hrs and 48 hrs, including targets of the well-known regulator NFκB.

Conclusions: This work shows that macrophages phagocytose arthroconidia, yet in the presence of macrophages, some arthroconidia are able to develop into the pathogenic host form of *Coccidioides*. We have created a foundation for better understanding the initial interactions between key host immune cells and the inhaled form of *Coccidioides*.

66TH ANNUAL COCCIDIOIDOMYCOSIS STUDY GROUP MEETING

DETECTION OF *COCCIDIOIDES* SPP. ON THE CHANNEL ISLANDS, CALIFORNIA

Julian Jordan, Antje Lauer
CSUB, Bakersfield, USA

INTRODUCTION: In coastal California, sea lions and other marine mammals, have occasionally been diagnosed with coccidioidomycosis, caused by the soil-borne fungal pathogen *Coccidioides* spp. which is endemic to the San Joaquin Valley of California and other areas in the Southwestern U.S. Though the presence of Valley Fever has been identified in numerous regions throughout the state, there has never been an attempt to detect *Coccidioides* on the Channel Islands which receive a substantial amount of dust deposits yearly from the mainland.

METHODS: A soil sampling plan (5-10 cm depth) was developed for Catalina Island, being the first island to be investigated, using information obtained from the United States Department of Agriculture (USDA) web soil survey database. Soil samples from areas near Avalon (n=36) and Two Harbors (n=42) were collected and analyzed for *Coccidioides* using a nested Polymerase Chain Reaction (PCR) approach. We are planning to expand this research by including soils from San Clemente Island and San Miguel Island in the future.

RESULTS: Out of 78 soil samples analyzed so far, several were positive for *C. immitis* (Avalon, n=1) and *C. posadasii* (Two Harbors, n=11).

CONCLUSION: Our results show that *Coccidioides* can be found in soils on Catalina Island. However further research needs to be completed to investigate if the pathogen is established on the island or if its presence can be explained by dust (or soil) deposits. The presence of *Coccidioides* spp. on the Channel Islands might pose a risk for humans vacationing on the island as well as terrestrial and marine mammals that can be found on or in the waters around the islands.

66TH ANNUAL COCCIDIOIDOMYCOSIS STUDY GROUP MEETING

FINDING LOVE IN DESPERATE CONDITIONS: SEX AS A RESPONSE TO NUTRIENT LIMITATION IN *COCCIDIOIDES POSADASII*

Klaire Laux[1], Marcus Teixeira[2,1], Bridget Barker[1]
[1]Northern Arizona University, Flagstaff, USA. [2]University of Brasilia, Asa Norte, Brazil

INTRODUCTION: Despite genetic evidence that sexual recombination likely occurs in *Coccidioides* spp. in the environment (Burt et al., 1996; Mandel et al., 2007) and the presence of unique structures produced in response to compatible mating types (Orr, 1968; Sigler et al., 1998), to date, no one has reliably produced and imaged structures associated with sexual recombination in *Coccidioides* spp. until now (Figure 1).

METHODS: Potentially compatible fungi were plated on different media types shown to be conducive to the mating process in other fungi. Fungi were selected from the first round of selection based on microscopic images indicative of the mating process and placed under harem mating conditions on different concentrations of nutrient availability.

RESULTS: Preliminary data show that in nutrient dense conditions, *Coccidioides posadasii* isolates undergo hyphal fusion (plasmogamy) but do not undergo the process of ascus and ascospore development. However, in nutrient-limited conditions, compatible fungi not only undergo plasmogamy and potential karyogamy, they also undergo the process of ascus and ascospore maturation within a cleistothecium-like structure that hardens and protects ascospores from adverse environmental conditions.

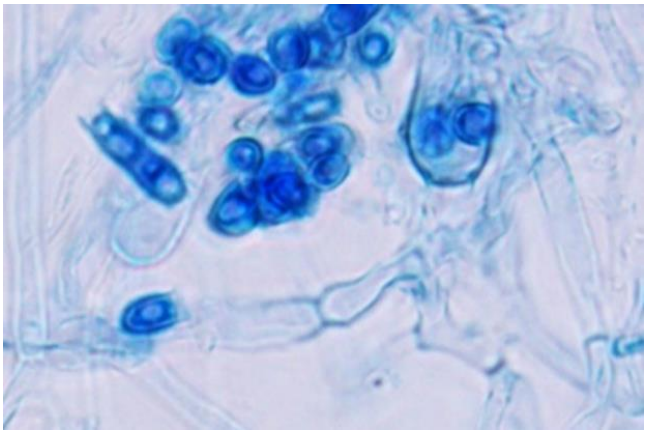

Figure 1 Mating structures of *Coccidioides posadasii* in the absence of Nitrogen or Carbon sources. Within the image include the vase-like vessels (asci) which contain meiospores (ascospores) and hyphal fusion (plasmogamy).

CONCLUSION: Viable ascospore production in response to nutrient-limited environments speaks to the possibility of climate change leading to novel variants of *Coccidioides* and may explain, in part, the recent rise in Valley Fever infections seen in Arizona and California (Centers for Disease Control and Prevention, 2021). Additionally, the hardiness of the cleistothecia produced during the process of sexual recombination may explain infections from areas not actively associated with animal burrows thus lending support for the endozoan, small-mammal reservoir hypothesis proposed by Taylor and Barker (2019).

66TH ANNUAL COCCIDIOIDOMYCOSIS STUDY GROUP MEETING

ESTABLISHMENT OF A *GALLERIA MELLONELLA* MODEL FOR THE STUDY OF VIRULENCE AND ANTIFUNGAL DRUG SUSCEPTIBILITY OF *COCCIDIOIDES*

Matthew Barker, Althea Campuzano, Sarah Saeger, Jieh-Juen Yu, Chiung-Yu Hung
UTSA Department of Molecular Microbiology and Immunology, South Texas Center for Emerging Infectious Diseases, San Antonio, USA

Introduction: *Galleria mellonella* has been employed for studying fungal pathogens such as *Candida*, *Aspergillus*, and *Cryptococcus*, but it has yet to be established for dimorphic fungal pathogens (i.e. *Coccidioides spp*). *G. mellonella* larvae possess a robust innate immunity comparable to vertebrates against fungal infections. In this study we evaluate the larva model for characterization of virulence factors and assessment of drug susceptibility against *Coccidioides* infection. Our objective is to establish the infection criteria of *G. mellonella* larvae with *Coccidioides* spores for high throughput screening of virulence factors and potential drug candidates against *Coccidioides*.

Materials and Methods: A clinical isolate of *C. posadasii* (C735) was used in this study in a BSL-3 laboratory. The larvae were purchased from a commercial source and stored at 20°C before use. Larvae (0.15-0.2g) were injected with 5-10x10^5 viable spores in 10 µl PBS by the haemocoel route and incubated at 37°C with 10% CO_2 for the period of the experiment. The larvae were measured for melanization production rates, histopathology, fungal burden and survival. The model then is applied for screening of *Coccidioides* mutants that were created by *Agrobacterium* (Ti plasmid) facilitated random gene disruption. C57BL/6 and BALB/c mice were challenged by the oropharyngeal aspiration with a suspension of potentially lethal dose of spores (450-470) prepared from the parental and the mutant strains. The larva model can also be used for validating newly discovered antifungal compounds *in vivo*. Drugs were administered via the haemocoel injections at a selected dose (1-, 2- and 5-fold) of minimal inhibition concentration (MIC) obtained using *in vitro* spherule cultures at 2, 48 and 96 hr postchallenge. Amphotericin B and PBS served as positive and negative controls, respectively.

Results: In the larva model, *Coccidioides spp.* can covert to parasitic growth and form spherules, the same morphotype in mammalian hosts. Surprisingly, the larvae were relatively resistant to *Coccidioides* infection compared to mice that have a LD_{100} of ~100 spores administrated by the oropharyngeal and intranasal routes. The infected larva survived for 2 and 4 days postchallenge with 1.0 and 0.5 million spores, respectively. Melanization score was peaked at 3 days postchallenge when they were challenged with a dose of 5x10^5 spores and allowed a longer period for evaluation of virulence and drug efficacy. Thus, it was the challenge dose used for subsequent experiments. We have identified 4 *Coccidioides* mutants that lost virulence in the larva model. Further evaluation of the mutants using a murine model of pulmonary coccidioidomycosis confirmed that the mutants were attenuated. Genomic sequence analysis of the mutant strain (*Cp*-30) revealed that a gene encoding for a 244-amino acid protein was disrupted. The *Cp*-30 mutant reduces conversion to parasitic spherules, while it appears to have normal saprobic growth. Furthermore, *in vivo* the *Cp*-30 mutant is highly attenuated in both the larva and murine models of coccidioidomycosis. Experiments are underway to characterize this virulence gene. Furthermore, we employed this larva model for assessing treatment efficacies of newly identified antifungal drugs from Broad Institute Repurposing drug library. Results demonstrated that 2 novel antifungal agents could prolong larva survival in a similar efficacy as Amphotericin B.

Conclusion: We have established a mellonella larva model of *Coccidioides* infection. Our findings suggest that *G. mellonella* is a useful model of coccidioidomycosis and convenient for pre-screening assays for the identification of fungal virulence factors and novel antifungal drugs.

66TH ANNUAL COCCIDIOIDOMYCOSIS STUDY GROUP MEETING

PREDICTION AND DISCOVERY OF *COCCIDIOIDES*-SPECIFIC T CELL EPITOPES

Nhung Nguyen[1], Althea Campuzano[1], Matthew Barker[1], Heidi Erickson[2], Josh Malo[2], Neil Ampel[2], Jane Homan[3], Chiung-Yu Hung[1]
[1]South Texas Center for Emerging Infectious Diseases. Department of Molecular Microbiology and Immunology, San Antonio, USA. [2]University of Arizona, Tuscon, USA. [3]Iogenestics, Madison, USA

Introduction: Vaccination against coccidioidomycosis is feasible as patients can develop life-long immunity to VF. Long-term memory to VF requires T helper cell (Th) activation by the major histocompatibility complex (MHCII) molecules expressed in antigen-presenting cells (APCs). Antifungal immunity is associated with mixed Th1- and Th17-type responses. We have used an immuno-bioinformatics platform to screen *Coccidioides* genomes and to predict potential T cells epitopes that are further validated using a human HLA-DR4 (DRB1*0401) transgenic mice and *ex vivo* recall assays using human PBMCs derived from healthy donors and VF patients. Our overall goal is to identify *Coccidioides*-specific epitope that can bind to human MHCII molecules and elicit T-cell mediated immunity.

Methods: We have applied an *in silico* approach using EigenBio software (IoGenetic LLC.) to predict potential Th epitopes from well-characterized *Coccidioides* antigens (Fast track) and from proteins that are highly expressed during the parasitic phase (Parasitic phase track). We first cloned, expressed, and purified recombinant proteins derived from *Coccididoides* and encapsulated them into glucan-chitin-particle adjuvant as a vaccine model. We evaluated T cell reactivity to the predicted synthetic peptide and peptide libraries using IFN-γ ELISA assays. Mice were vaccinated three times with either the full-length protein or adjuvant control then tested for in vitro recall response to synthetic peptides representing the predicted epitopes (15-mer to 25-mers, GenScript). Lymphocytes were isolated from the spleens of immunized HLA-DR4 mice (n= 4-5 mice per group). Furthermore, we utilized an *ex vivo* approach to validate human cell immunity by co-culturing autologous $CD4^+$ T cell and APCs of healthy donors in the MiMIC system (Sanofi) as well as cytokine recall assays in patient samples.

Results: We completed bioinformatics analysis for 10 well-characterized fast-track antigens and ~200 coccidioidal proteins that are shown to be highly expressed in the parasitic phase. We identified 17 IFN-γ-stimulating epitopes from 6 fast-track coccidioidal antigens for the HLA-DR4 allele using the transgenic mice. Currently, 18 of the 20 VF recovering patients have a Stimulation Index greater than 1 and recognize the multivalent antigen (rCpa1), and they are reactive with one or more of the identified epitopes. Parallelly, these antigens and peptides are under evaluation using an *ex vivo* T cell assay platform called MiMIc provided by Sanofi using primed DCs and Th cells isolated from healthy donors. Additionally, we obtained control blood samples from healthy donors outside the historical endemic area. Comparison of IFN-γ expression amounts from the VF patients (n=19) versus the healthy subjects (n=16) is significant ($P < 0.05$).

Conclusions: We have successfully established a bioinformatics prediction in conjunction with *ex vivo* T cell-recall assays to identify short peptides (17-28 aa) of Coccidioides antigens that can stimulate IFN-γ production. These short peptides are deposited in the public immune epitope database (IEDB) that can be used to facilitate the development of diagnostic kits and vaccine antigens.

66TH ANNUAL COCCIDIOIDOMYCOSIS STUDY GROUP MEETING

ASSESSMENT OF SPATIOTEMPORAL DISTRIBUTION OF *COCCIDIOIDES* WITHIN AMBIENT AIR IN PHOENIX, AZ

Parker Montfort[1], W. Tanner Porter[1], Daniel Lord[1], Lalitha Gade[2], Anastasia Litvintseva[2], Jolene Bowers[1], David Engelthaler[1]
[1]Pathogen and Microbiome Division, Translational Genomics Research Institute (TGen North), Flagstaff, USA. [2]Mycotics Disease Branch, Centers for Disease Control and Prevention, Atlanta, USA

Introduction: While aerosolization of *Coccidioides* arthroconidia is a driver of Valley Fever infections, a limited amount of research has focused on characterizing the spatial and temporal distribution of arthroconidia within the ambient air. Where and when *Coccidioides* is airborne is crucial to accurately understand and model the complex dynamics of this endemic pathogen at both a local and regional level.

Methods: Portable air sampling units were used for air sampling across a 24-hour period across 23 sites in the Phoenix metropolitan area. Daily collections over a 30-month period were conducted as part of an ongoing surveillance in collaboration with the U.S. Department of Homeland Security, AZ Department of Health Services and the Centers for Disease Control and Prevention. DNA was extracted from air filters using Qiagen DNeasy PowerLyzer PowerSoil kits and DNAs were screened for *Coccidioides* DNA using previously published molecular techniques.

Results: In total, between TGen and the CDC, 9361 filters were collected from July 2017 through December 2019 and 5480 have been screened for the presence of *Coccidioides*. Across 5465 tested samples, a total of 394 were positive for *Coccidioides* DNA. Of the 23 sites, 5 had no detected positives, and the remaining 18 sites had an average prevalence of 3.7%. One site in particular stood out as a hot spot, with a 21.8% prevalence rate, well above the range of 0.6-6.4% observed in the other positive sites.

Conclusion: Our data suggest an uneven distribution of *Coccidioides* bioaerosols in the Phoenix metropolitan area, ranging from areas with no detected fungus to distinct “hot-spots.” Such findings support our hypothesis that local factors are involved in the aerosolization of arthroconidia and may help drive potentially different disease risk levels within the city. Our next steps aim at examining the association of the supposed drivers and detectable *Coccidioides* within ambient air.

66TH ANNUAL COCCIDIOIDOMYCOSIS STUDY GROUP MEETING

URGENT CARE PRACTICE PATTERNS FOR DIAGNOSING COCCIDIOIDOMYCOSIS IN A HIGHLY ENDEMIC URBAN POPULATION.

Jie Pu, Valerie Miranda, Devin Minior, Shane Reynolds, Benjamin Rayhorn, and John N Galgiani.

INTRODUCTION: We found previously that very few urgent care (**UC**) patients (**pts**) were diagnosed with coccidioidomycosis (**CM**). Since 2020, during onboarding, at quarterly meetings, and in periodic emails, we have encouraged UC clinicians to more frequently test for CM for pts with pneumonia (**PNA**)when appropriate.

METHODS: Banner UC clinics have increased to n=48 by 2021 with now a staff of over 250 clinicians. Installation and training of a common electronic medical record was completed in 2017. In March 2022, a data download was created for this analysis of UC clinician patterns of coccidioidal serologic testing (**CST**, mostly EIAs), CST results, and their relation to patient ICD10 profiles.

RESULTS: For the years 2018-19 (787K UC visits) and 2020-21 (1,290K UC visits), CSTs were ordered per 10^4 visits 6.1 and 17.8 times, respectively (chi-squared $p<0.0001$). Positive CST were highest for August, November and January (17.0%) and lowest for other months (10.6%). Among ICD10 codes most frequently associated with positive CST visits were PNA (n=187), cough (n=174), fever (n=63), bronchitis/URI (n=43), and *Erythema nodosum* (**EN**, n=27). Of 176 EN pts, only 6 also had PNA. During the study period, pts with PNA had increased CSTs overall, CSTs on the first visit, and CSTs on the second visit when the first visit was negative. For EN pts, 61% had positive CST. With increased clinician reminders, the frequency of CTS of pts with PNA has increased three-fold, but still CST is done in less than three-quarters of pts where recommended.

CONCLUSION: Routine quality improvement activities have significantly but only partially improved rates of testing pts with PNA for CM in UC clinics located in a highly endemic area. Innovative strategies may be needed to improve current practice. Also in our region, EN, independent of PNA, is a strong predictor of CM.

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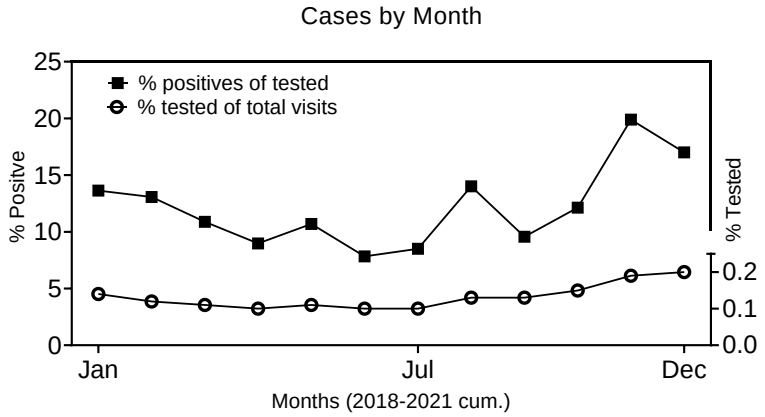
Results	2018	2019	2020	2021
Total UC patients (thousands)	373	414	593	698
Total UC pts with PNA	2,094	2,565	3,473	3,558
PNA pts with CST	7.2%	7.9%	21.1%	22.0%
1st visit # tested (% pos.)	21 (29%)	45 (29%)	478 (20%)	543 (13%)
2nd visit # tested (% pos.)	129 (14%)	157 (18%)	254 (31%)	238 (16%)
Both visits # tested (% pos.)	2 (100%)	3 (0%)	39 (41%)	45 (62%)
PNA pts with positive CST	17.3%	20.8%	26.0%	17.5%
Total UC pts with EN	21	44	58	53
EN pts with CST	9.5%	25%	24%	32%
EN pts with positive CST	50%	55%	71%	59%

Figure. Frequency of testing for CM in all visits and percentage of tests that were positive in BUCS by month for the years 2018-2021.



COCCIDIOIDOMYCOSIS OF THE SPINAL CORD - ANALYSIS OF 19 CASES AND REVIEW OF THE LITERATURE

Rasha Kuran[1,2], Manan Thacker[1,2], Rupam Sharma[1,2], Arman Froush[1], Royce Johnson[1,2], Arash Heidari[1,2]
[1]Kern Medical, Bakersfield, USA. [2]Valley Fever Institute, Bakersfield, USA

Introduction: Central nervous system involvement with coccidioidomycosis is a serious infection that is universally fatal if not treated. Prior to the advent of MRI, very few reports described spinal cord involvement and autopsies often omitted spinal cord examination. Accurate localization of the anatomic location affected by CNS cocci at initial diagnosis can be challenging due to mental status changes and the presence of brain abnormalities. At the Valley Fever Institute we adopted the practice of performing MRI imaging on the entire neuro-axis at the time of diagnosis. Here we describe the radiologic and clinical characteristics of 19 cases of CNS cocci who had spinal MRI imaging performed

Methods: This study was approved by Kern Medical Institutional Review Board. ICD 9 and ICD 10 codes were used to query Valley Fever Institute and KM's electronic health record for a period of ten years. Patients were included if they qualified for the diagnosis of probable CNS coccidioidomycosis and had Magnetic Resonance Imaging performed on their spinal cord

Results: The majority of patients studied had abnormal spinal imaging. Arachnoiditis being the most common, followed by myelitis, spinal abscess and syringomyelia. Interestingly, spinal cord abnormalities can be asymptomatic. Most common symptom was back pain followed by radiculopathy

Conclusion: Coccidioidal meningitis frequently involves the spinal cord. Radiologic findings include leptomeningeal enhancement, adhesive arachnoiditis with nerve root clumping, myelitis and syringomyelia. Heightened awareness is required due to unpredictable symptomatology

66TH ANNUAL COCCIDIOIDOMYCOSIS STUDY GROUP MEETING

STRUCTURAL AND FUNCTIONAL STUDIES OF *COCCIDIOIDES* CPS1

M. Alejandra Mandel, Devin K. Seka, Christine D. Butkiewicz, Nitesh K. Khandelwal, Hien T. Trinh, Lisa F. Shubitz, John N. Galgiani, Thomas M. Tomasiak, Marc J. Orbach
University of Arizona, Tucson, USA

INTRODUCTION: A live-attenuated coccidioidomycosis canine vaccine has been developed based on a *Coccidioides posadasii* Silveira mutant with a *CPS1* gene deletion. The mutant strain fails to produce mature spherules and is avirulent even in immunodeficient mice indicating it's safety. To understand why the *CPS1* deletion is so debilitating, we are defining the structural and functional domains of the protein the role of *CPS1* in normal growth and spherulation of *Coccidioides*.

METHODS: To define the role the domains Cps1 have in spherulation, derivatives of *C. posadasii* strain Silveira expressing domain deletion derivatives of *CPS1* were created and screened for virulence in a mouse infection model and for in vitro spherulation. An avirulent Δ*cps1*::Bleo strain was created to be used as a recipient for mutated *CPS1* genes. Three domain deletion constructs of *CPS1* were created, each with a deletion of a single conserved domain, the 67 amino acid DMAP1b domain, or one of the two adenylate-forming domains, AMP1 (302 amino acids) or AMP2 (452 amino acids). Gene constructs were tagged at the C-terminus with in-frame c-myc and His tags for validation of protein expression. The domain deletion constructs, containing the *hphR* gene were transformed into the Δ*cps1::Bleo* strain selecting for hygromycin resistance. Transformed strains were purified and screened by antibiotic resistance, PCR and DNA hybridization to confirm insertion of the gene deletion construct at the *CPS1* locus by replacement of the *BleoR* marker. Virulence studies were performed using C57BL/6 mice (8 mice per strain) with lung and spleen fungal burdens compared by Kruskal-Wallis. To demonstrate expression of the *CPS1* domain deletion proteins, Westerns were performed on protein extracts and analyzed by c-myc antibody screening.

Protein prediction programs have suggested that Cps1 is a transmembrane protein. For structural characterization of Cps1, *CPS1* cDNA copies containing an N-terminal FLAG tag and a C-terminal His tag, were expressed in *Saccharomyces cerevisiae* plasmid 83nu under the control of the inducible *GAL1* promoter. Protein purification was performed by lysis of induced cells followed by membrane purification and extraction with different detergents. Efficiency of protein solubilization following detergent extraction was determined by Western analysis of membrane supernatant and pellet fractions using anti-FLAG or anti-His antibodies. The structure of Cps1 was analyzed recently using AlphaFold2.1, the AI-based protein structure prediction program developed by Google's Deep Mind.

RESULTS: Deletion of either of the two Cps1 adenylate-forming domains, AMP1 or AMP2, resulted in strains that reiterated the Dcps1 phenotype; they were avirulent and failed to persist in mice. Deletion of the Cps1 DMAP1b domain produced strains that were fully virulent in mice. Western analysis demonstrated that the proteins were expressed in the transformed strains. Although previous protein structure programs predicted Cps1 contains between four and seven transmembrane domains, AlphaFold2.1 predicts that Cps1 lacks transmembrane domains and is a globular peripheral membrane protein. The Cps1 globular prediction indicates positively charged patches of amino acids complimentary to the negative head groups of membrane lipids. Recombinant Cps1 shows limited solubilization from the membrane fraction using a variety of membrane solubilization detergents. In contrast, a high salt (1 M NaCl) extraction without detergents resulted in recovery of the highest levels of Cps1. AlphaFold2.1 also predicts a conserved ATP binding domain that corresponds to part of the AMP2 domain in Cps1.

CONCLUSION: Mouse studies and in vitro spherulation demonstrate that the two catalytic adenylation domains of Cps1 are critical for spherulation and virulence, while the DMAP1 binding domain is dispensable. This indicates that the catalytic activity of Cps1 is important for Cps1 function. Predictions and preliminary binding studies connect the catalytic activity of AMP2 with ATP binding. Understanding the targets of Cps1 that result in the profound spherule defect of *CPS1* mutants will aid our understanding of parasitic phase development.

66TH ANNUAL COCCIDIOIDOMYCOSIS STUDY GROUP MEETING

PROTECTIVE HOST RESPONSES AGAINST *COCCIDIOIDES**

Susana Tejeda-Garibay, Anh Diep, Nadia Miranda, Katrina Hoyer
University of California Merced, Merced, USA

*Did not wish to publicly release abstract

66TH ANNUAL COCCIDIOIDOMYCOSIS STUDY GROUP MEETING

INTERACTIONS BETWEEN VALLEY FEVER AND GENETIC ANCESTRY: DOES GENETIC ANCESTRY AFFECT RISK OF DEVELOPING DISSEMINATED COCCIDIOIDOMYCOSIS?

Sarah J. Spendlove[1,2], Samantha L. Jensen[3], Diego Orellana[2,4], Alexis V. Stephens[5], George R. Thompson[6,7,8], Royce H. Johnson[9,10], Arash Heidari[9,10], Manish J. Butte[3,5], Valerie A. Arboleda[1,2,3,11]
[1]Interdepartmental Bioinformatics Program, David Geffen School of Medicine, UCLA, Los Angeles, CA, USA. [2]Department of Pathology and Laboratory Medicine, David Geffen School of Medicine, UCLA, Los Angeles, CA, USA. [3]Department of Human Genetics, David Geffen School of Medicine, UCLA, Los Angeles, CA, USA. [4]UC Santa Barbara, Santa Barbara, CA, USA. [5]Division of Immunology, Allergy, and Rheumatology, Department of Pediatrics, David Geffen School of Medicine, UCLA, Los Angeles, CA, USA. [6]UC Davis Center for Valley Fever, UC Davis, Davis, CA, USA. [7]Department of Medical Microbiology and Immunology, UC Davis, Davis, CA, USA. [8]Department of Medicine and Division of Infectious Diseases, UC Davis, Davis, CA, USA. [9]Department of Medicine, David Geffen School of Medicine, UCLA, Los Angeles, CA, USA. [10]Valley Fever Institute, Kern Medical, Bakersfield, CA, USA. [11]Department of Computational Medicine, David Geffen School of Medicine, UCLA, Los Angeles, CA, USA

INTRODUCTION: Coccidioidomycosis, commonly known as "Valley Fever," is an endemic fungal infection in the Southwest part of America. The majority of patients are asymptomatic after infection or develop only a respiratory infection. However, a rare fraction of individuals go on to develop severe disseminated coccidioidomycosis (DCM), which is associated with significant morbidity and mortality and requires prolonged and sometimes lifelong antifungal treatment. The factors that contribute to an individual's risk for developing DCM are multifactorial, however, the genetic basis of this risk remains unclear.

METHODS: Both rare and common genetic variants have been shown to contribute to infection severity in a variety of infectious diseases, including herpes encephalitis, COVID-19 and tuberculosis. Early epidemiological studies for coccidioidomycosis have also identified an association of self-identified race and ethnicity with the risk of DCM. We obtained whole exome sequencing data from 479 individuals with coccidioidomycosis from the UC Davis Center for Valley Fever.(468 individuals after quality control). This cohort includes a mixture of both severe and mild coccidioidomycosis, including 109 individuals who developed DCM. We also obtained whole genome sequencing from 87 individuals with coccidioidomycosis and blood RNA-seq data for a subset of this group (n= 42) from the Valley Fever Institute at Kern Medical. We plan to use these data to validate our preliminary results from the exome data and investigate expression and splicing differences associated with genetic ancestry. We determined genetic ancestry through PCA analyses then ran ADMIXTURE mapping with k=4 to determine global ancestry proportions. We then calculated odds ratios of DCM compared to what we classify as Uncomplicated Valley Fever (UVF) dependent on global ancestry proportions.

RESULTS: We find through PCA analyses that patients with African genetic ancestry have an increased chance of having DCM in our cohort. To further investigate this signal, we looked at global ancestry proportions. Using unsupervised ADMIXTURE mapping we found that the global ancestry of our exome patients can be divided into 4 subgroups.

The first subgroup, k1, is closely associated with African genetic ancestry. 95% of the individuals who were identified as being of African genetic ancestry through PCA analyses (63, or 13.5% of our cohort) had over 50% of their global ancestry represented by k1, and no patients with over 50% of their global ancestry represented by k1 were identified as not being of African genetic ancestry. Odds ratio analyses show that individuals with 100% k1 global ancestry had 17 odds of DCM vs UVF (p=1.7e-12).

The fourth subgroup, k4, is closely associated with European genetic ancestry. 100% of the 162 individuals who were identified as being of European genetic ancestry through PCA analyses had over 63% of their global ancestry represented by k4. An additional 23 patients had over 50% of their global ancestry represented by k4, bringing the total number of our cohort with over half k4 global ancestry to 185, or 40% of our cohort. Odds ratio analyses show that individuals with 100% k4 global ancestry had 0.25 odds of DCM vs UVF (p=9.7e-7).

Thus, we show through ADMIXTURE mapping and an odds ratio analysis that the k1 portion of the genome, which is associated with patients of African genetic ancestry, carries an increased risk of DCM, while the k4 portion of the genome, which is associated with patients of European genetic ancestry, carries a decreased risk of DCM. In the future, we plan to do supervised ADMIXTURE analyses as well as local ancestry analyses to further investigate these results. We also plan to validate our results with the 87 genomes from the Valley Fever Institute. RNAseq from some of the genome-sequenced individuals (n=42) will be used to interrogate the pathways that explain this association.

CONCLUSION: Our work described here confirms that African genetic ancestry is an independent risk factor for DCM status in this specific cohort. Future work will investigate whether this is replicated in an independent cohort from the Valley Fever Institute. This project has the potential to help us develop genetic biomarkers to identify individuals at the highest risk for DCM and those who would benefit from early treatment with immunomodulatory therapies.

66TH ANNUAL COCCIDIOIDOMYCOSIS STUDY GROUP MEETING

SERUM PROCALCITONIN LEVEL IN PULMONARY COCCIDIOIDOMYCOSIS INFECTION

Shatha Aboaid[1], Rupam Sharma[2], Arash Heidari[3,4,2], Ayham Aboeed[3,5]
[1]Department of Medicine, Kern Medical Center, BAKERSFIELD, USA. [2]Valley Fever Institute, Kern Medical Center, BAKERSFIELD, USA. [3]Department Of Medicine, Kern Medical Center, BAKERSFIELD, USA. [4]Division Of Infectious Disease, Kern Medical Center, BAKERSFIELD, USA. [5]Division Of Pulmonary and Critical Care, Kern Medical Center, BAKERSFIELD, USA

Introduction: Procalcitonin, the peptide precursor of calcitonin, was first studied as a biomarker in acute severe bacterial infections in 1993 and has been deemed helpful in differentiating between bacterial and viral infections. Procalcitonin has been useful as an adjunct to clinical judgment for guiding antibiotic therapy and its discontinuation. It has been best studied in distinguishing between viral and bacterial lower respiratory infections. The relationship between serum procalcitonin levels and primary coccidioidomycosis was initially studied by Sakata et al. in 2014 and did not reveal a relationship between elevated procalcitonin and coccidioidal infection. The purpose of this study was to determine any association between serum procalcitonin levels and primary pulmonary coccidioidomycosis.

Methods: We conducted a retrospective chart review study using the Valley Fever Institute database between 2017 and 2021. This study was approved by the Kern Medical Institutional Review Board. The literature search was conducted on PubMed and Google scholar using coccidioidomycosis; community-acquired pneumonia; procalcitonin levels as keywords. Coccidioidomycosis infection was confirmed by serology, or microbiology of sputum or broncho-alveolar lavage, and radiological evidence of pneumonia. Bacterial infections were excluded by reviewing the results of sputum and blood cultures.

74 patients were enrolled during in-patient care. We identified 52 patients with acute infection and 22 patients with chronic infection. Acute infection was defined as new symptomatic primary pulmonary coccidioidomycosis of < 6 weeks' duration. Chronic infection was defined as either proved previous coccidioidomycosis infection or pneumonic symptoms of ≥ 6 weeks' duration. The first value of the procalcitonin assay, with a cutoff of > 0.10 μg/L being positive.

Results: Of all patients with acute infection 34 (65.38%) had a positive test for Procalcitonin as compared to 12 (54.54%) for the Chronic patients. The odds ratio is 1.57 suggesting a greater incidence of positive procalcitonin among acute patients; however, the finding is not statistically significant ($p = 0.3811$).

Conclusion: This study did not find the clinical value of procalcitonin in the diagnosis of pulmonary coccidioidomycosis or differentiating acute from chronic infection. Procalcitonin does not distinguish bacterial pneumonia from coccidioidal pneumonia. Further larger randomized controlled studies are needed to investigate this relationship. Clinicians should continue to use clinical judgment and laboratory as well as imaging to distinguish pulmonary coccidioidomycosis vs. bacterial pneumonia.

66TH ANNUAL COCCIDIOIDOMYCOSIS STUDY GROUP MEETING

IMPACT OF VALLEY FEVER ON QUALITY OF LIFE

Kathy T. Nguyen[1], Alexis V. Stephens[2], Dana Brucker[3], Royce H. Johnson[3], Manish J. Butte[2], Morna J. Dorsey[1]
[1]University of California, San Francisco, San Francisco, USA. [2]University of California, Los Angeles, Los Angeles, USA. [3]Kern Medical, Bakersfield, USA

INTRODUCTION: Valley Fever (VF) infection can cause significant chronic disease. Impact on quality of life is poorly understood across disease severity.

METHODS: An IRB approved survey was designed by VF care providers at the Valley Fever Institute (VFI), UCLA, and UCSF. After obtaining informed consent, the survey was performed during routine in-person visits at the VFI from March 2020 to March 2021. Major topics in the questionnaire included quality of life, social determinants of health, and barriers to receiving treatment. VF infection category, and VF infection type were compared across survey results and demographics using Fisher's exact test and Chi-squared tests.

RESULTS: The survey was administered at the VFI to 83 adult participants with a mean age of 45.9 years. 53.2% were male, 69.6% Hispanic/Latino, 20.3% white, 3.8% African American/black, 2.5% Asian, and 2.5% Pacific Islander. Cohort VF category and infection type are summarized in Table 1.

Table 1. Participant Valley Fever Classifications

Classification	(%)
VF Category (n=76)	
Complicated VF	47.4%
Uncomplicated VF	52.6%
VF Infection Type (n=79)	
Mild pulmonary	55.7%
Severe pulmonary	5.1%
Meningitis	32.9%
Single skeletal	7.6%
Multi-bone disease	5.1%
Other	7.6%

41.7% (n=35) of participants reported hospitalizations within the past 12 months, with 57.1% (n=20) of these hospitalizations related to their valley fever. 51.2% (n=42) report experiencing at least moderate fatigue over the past seven days. 41.3% (n=33) rate their physical health as fair or poor. 48.2% (n=39) report at least moderate limitation to their normal physical activity due to VF. Similarly, 35.1% (n=28) experience at least frequent work difficulties. 53.8% (n=43) agree VF has prevented them from maintaining employment. Of those currently not working 63% (n=51), 62% (n=31) report cause as due to illness/ disability. Four (4.9%) participants revealed there are barriers to receiving treatment for VF and cited financial, insurance issues and provider lack of knowledge as factors. Males had significantly higher job losses from VF (p=0.011). Females reported significantly worse mental health (p=0.016). Participants with complicated VF infection report worse quality of life (p=0.020), lower satisfaction with their social activity (p=0.063), decreased ability to carry out their day-to-day activities (p=0.065). Participants with mild pulmonary type VF report significantly better general health (p=0.013), mental health (p=0.032), overall quality of life (p=0.0026), improved ability to carry out their day-to-day activities (p=0.024) and higher satisfaction with their social activities (p=0.034).

CONCLUSION: This survey characterizes the impact of VF on quality of life across highlights the importance of psychosocial support to ensure patient health and quality of life can be optimized.