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# Impact and Control of Valley Fever: Proceedings of a Workshop in Brief (2023)

## DETAILS

13 pages | 8.5 x 11 | PDF

ISBN 978-0-309-70149-5 | DOI 10.17226/26928

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## SUGGESTED CITATION

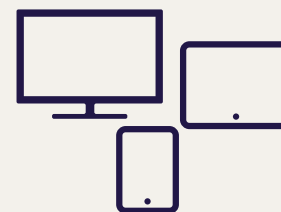
National Academies of Sciences, Engineering, and Medicine. 2023. *Impact and Control of Valley Fever: Proceedings of a Workshop in Brief*. Washington, DC: The National Academies Press. <https://doi.org/10.17226/26928>.

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# Impact and Control of Valley Fever

## Proceedings of a Workshop—in Brief

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On November 17 and 18, 2022, the Board on Global Health of the National Academies of Sciences, Engineering, and Medicine hosted an in-person and virtual workshop to review the epidemiology of coccidioidomycosis (Valley fever), its impact on populations, and currently available diagnostic and treatment options. The workshop also explored prospects for control of the disease through vaccination. This Proceedings of a Workshop—in Brief highlights the presentations and discussions that occurred during the workshop. The contents of this document are based on the discussion of the individual workshop participants and should not be misconstrued as consensus.

### BACKGROUND

During the first session, Joshua D. Nosanchuk from the Albert Einstein College of Medicine provided an overview of the role of fungi in the environment. Ubiquitously present in our environment, fungi play beneficial roles but are also responsible for a significant burden of disease, he noted. An estimated 300 million people around the world have serious fungal infections (GAFFI, 2022). Invasive mycoses contribute to approximately 1.5 million human deaths each year and are financially costly (Rayens and Norris, 2022). Nosanchuk noted that climate change shifts the geographic spread of

pathogens, including fungi. In 2022 the World Health Organization presented a fungal priority pathogen list, including *Coccidioides* spp., which is considered in the medium priority category (WHO, 2022). *Coccidioides* spp. are dimorphic organisms that occur naturally in soil. They can infect humans via the respiratory tract after disturbances in the soil. Coccidioidomycosis, or Valley fever, is caused by two highly similar fungi species: *Coccidioides immitis* and *Coccidioides posadasii*. About 40 percent of people will develop symptoms such as fever and cough. About 5–10 percent of people will have a more serious disease, such as pneumonia. Approximately 1 percent of people will develop serious disease, including meningitis (CDC, 2020). In 2019 there were about 20,000 reported patients in the United States of America. 95 percent of U.S. cases are found in southern Arizona and the San Joaquin Valley region in California. There are about 200 deaths annually due to Valley fever, and hospitalization costs are high (CDC, 2022). Additionally, coccidioidomycosis is a significant cause of morbidity and mortality in various animals. Nosanchuk emphasized the importance of addressing this disease.

Neil M. Ampel from the University of Arizona and the Mayo Clinic in Arizona Care System provided more detail on human coccidioidomycosis. He explained

that while most individuals who acquire infection will be asymptomatic and develop lifelong immunity to further infection, about 40 percent of infections lead to primary pulmonary infection, presenting with cough, chest pain, fever, and immunological events that may cause morbidity. Diagnosis is often delayed, as there is no point-of-care test for coccidioidomycosis, Ampel explained. Some patients develop non-meningeal extrathoracic dissemination, generally within six months of the initial infection. A smaller group of patients may develop meningeal dissemination, which is deadly if it remains untreated. These patients are at risk for prolonged disease with complications that require close clinical follow-up, antifungal therapy, or surgical intervention. Current therapies often must be taken for long periods of time (in the case of meningitis, for the rest of the patient's life) and are associated with a high rate of relapse after discontinuation.

The burden of human disease was further emphasized by Monk Yun Rou, who joined the meeting to discuss his personal experience with the disease, highlighting its severity and chronicity. As with many other patients, his disease was initially misdiagnosed. Following diagnosis with coccidioidomycosis, he received treatment for meningitis but suffered adverse effects from the drugs. He then entered a clinical trial and began treatment with an experimental drug, which was more tolerable. Besides coccidioidomycosis, he developed long COVID during the COVID-19 pandemic. Monk Yun Rou highlighted that the disease results in significant suffering. With low energy levels, he requires a lot of sleep and rest throughout his day and activities of daily living are severely affected. It is distressing for patients to compare how they used to live versus what life is like with coccidioidomycosis, Monk Yun Rou expressed.

In addition to the personal burden the disease causes, significant economic costs are associated with Valley fever. George W. Rutherford from the University of California, San Francisco, presented an overview of the economic costs of coccidioidomycosis based on a literature review. Observations of direct medical costs per person are consistent across two studies from California and one study from Arizona and vary between \$55,000

and \$65,000 (Grizzle et al., 2021; Sondermeyer et al., 2013; Wilson et al., 2019). Deducting data from these studies and the total reported cases to the CDC in 2019 (20,003 cases; CDC, 2022), Rutherford calculated the lifetime direct medical costs associated with this one-year cohort of cases to be \$1.125 billion.

Besides humans, coccidioidomycosis is also a threat to animals. Jane E. Sykes from the University of California, Davis, discussed how increased exposure to *Coccidioides* spp. can affect companion animals, production animals, and wildlife. Many infections go undetected, and improved surveillance and reporting are urgently needed, said Sykes. Animal owner education in endemic regions can help achieve that goal. She also explained that animal disease offers detection opportunities, such as providing a sentinel effect; for example, infection in dogs may warn of local endemicity, as dogs are at high risk due to their digging behavior. Predictive maps for canine infections closely align with similar maps for human cases (Grayzel et al., 2017). Furthermore, animals can be used as models for diagnosis and treatment studies, and prevention of animal infections could aid in slowing the spread of *Coccidioides* spp.

Paris Salazar-Hamm, University of New Mexico, discussed her wildlife surveillance research. Since animal infection may provide some clues for the endemicity of *Coccidioides*, Salazar-Hamm researched *Coccidioides* presence in lung tissues of small mammals from museum samples (Salazar-Hamm et al., 2022). *Coccidioides* spp. were detected in 14 species of small mammals in 12 percent of total samples explored. Collections suggest locally acquired *Coccidioides* in California, Arizona, and New Mexico counties. In mammals, *Coccidioides* was in low relative abundance, and its presence did not appear to disrupt the normal lung mycobiome, suggesting it could be commensal in these animals. Salazar-Hamm highlighted the importance of biorepositories in disease research and surveillance.

#### **SURVEILLANCE AND CHARACTERISTICS OF SPREAD**

John W. Taylor from the University of California, Berkeley, discussed the life cycle of *Coccidioides* and how it was once considered primarily a disease of rodents,

with rodents as a natural reservoir (Emmons, 1943). In the 1950s an environmental cycle hypothesis emerged, in which the local small mammals were considered accidental hosts. Genomics of *Coccidioides* revived the central role of rodents and led Taylor and Bridget Barker to propose the endozoan hypothesis (Sharpton et al., 2009; Taylor and Barker, 2019). In this hypothesis, *Coccidioides* arthroconidia enter the small mammal by inhalation and transform into spherules, which are most often contained in the host granuloma with no disease, although spherules can release endospores leading to death. In either case, once the rodent dies, hyphae grow in the carcass and produce new arthroconidia, which infect naïve hosts via short-distance dispersal from soil or long-distance dispersal from air. These arthroconidia infect humans, but owing to burial practices, humans are dead ends. This hypothesis is supported by data that show native rodents and their burrows harbor *Coccidioides* (Kollath et al., 2020; Salazar-Hamm et al., 2022). Transmission to humans by excavation of soil from undisturbed habitat is well documented by disease outbreaks among workers. Transmission over long distances by air is suggested by the similarity of assemblages of airborne fungi over both undisturbed habitat and agricultural fields (Wagner et al., 2022). Several high-priority challenges remain, including developing effective air sampling for *Coccidioides* and understanding the details of *Coccidioides* transmission among native rodents.

Mitsuru Toda from the Centers for Disease Control and Prevention discussed current surveillance and incidence of human disease. Although Valley fever is nationally notifiable in the United States, it is only reportable in approximately half of the states. Outside the United States, it is only reportable in Guatemala and one state in Argentina. Due to surveillance challenges, the burden of symptomatic cases is estimated to be 33 times more than what is reported nationally. In the United States, efforts are under way to implement national fungal surveillance through FungiSurv in collaboration with state public health partners, Toda remarked. Toda also stated that CocciHub, a collaborative hub for predictive modeling, will bring modelers, public health partners, and subject matter experts together to advance efforts to forecast

disease risk and predict endemicity for Valley fever. Besides underreporting, Valley fever is underdiagnosed, Toda stated. As the disease is often mistaken for other conditions, people often seek health care multiple times before being tested for Valley fever, with a median time to diagnosis of 38 days, said Toda. Therefore, 70 percent of patients have other conditions diagnosed first, which in many cases leads to unnecessary antibacterial treatments (Benedict et al., 2019).

Gail Sondermeyer Cooksey discussed work she and colleagues are performing at the Division of Communicable Disease Control of the California Department of Public Health (CDPH). Valley fever is endemic in California, and rates have increased significantly over the past 10 years. Rates vary widely between regions, with the vast majority occurring in the Southern San Joaquin Valley. However, Cooksey's research shows that in recent years Valley fever rates have increased more in regions outside of the highest incidence region. Infection is more commonly reported in men. Most patients are between ages 40 and 79, though age risk varies by region. Higher case rates are also seen in Black people throughout the state, and Hispanic/Latino people were found at higher risk in certain regions. Possible causes for increases in Valley fever cases in different regions are winter rains after drought, climatic factors, soil disturbance activities, susceptible people moving into endemic regions, and increased reporting and recognition. Generally, higher rates of Valley fever are detected after droughts, and the increase is greatest in wetter areas. Cooksey stated that with climate extremes, Valley fever's endemicity will likely expand. A limited survey from 2017 suggests that only 42 percent of Californians are aware of Valley fever, which poses a challenge to outreach (Hurd-Kundeti et al., 2020). Furthermore, Cooksey stated that awareness among physicians in the United States outside of California and Arizona is likely limited. CDPH has increased efforts to raise awareness among health care providers and the public, but it has been challenging to get the information to the intended audiences.

Shane Brady from the Arizona Department of Health Services followed up on the epidemiology in Arizona.

Most Arizona cases (94 percent) are found in the three most populous counties (Maricopa, Pima, and Pinal). The highest number of cases are seen among those aged 65–74 years, and males accounted for about half of the cases, he stated. Hospitalization costs are high, and a large increase in deaths was seen in 2020, which may be related to the COVID-19 pandemic. Generally, large increases in cases are detected in fall and winter. To perform enhanced surveillance, patients were contacted by phone to further assess diagnostic and awareness issues. Patients were symptomatic for a median of four months, 41 percent were hospitalized, and many sought medical care multiple times. Of all patients, 75 percent missed work for a median of two weeks, and 75 percent were not able to do activities of daily living for a median of six weeks, Brady said. The median time between the first health care visit and correct diagnosis was 23 days for the interviewed patient group. People who were aware of the disease were more likely to receive an earlier diagnosis, as they were more likely to ask for Valley fever testing. Therefore, several campaigns have been initiated in Arizona to increase public and physician awareness, including a yearly Valley fever awareness week. Since Valley fever cases in Arizona have been increasing significantly in recent years, improved education for the public and health care providers is critical for reducing delays in diagnosis and improving health management, Brady concluded.

Morgan E. Gorris from Los Alamos National Laboratory discussed her research on climate change and how it affects Valley fever epidemiology. *Coccidioides* spp. grow primarily in semi-arid environments. Gorris's research suggests that as climate change progresses, there is increased risk that *Coccidioides* will be able to spread farther north, increasing the range of endemicity across the western United States. Increased soil disturbance allows spores to spread, and rodent movement may also cause the fungus to move into new areas. Increased dust storms resulting from climate change could also be a mechanism for spread. Disease surveillance is essential to understand who is at risk and to mitigate the negative health effects of Valley fever. Stages of the *Coccidioides* life cycle are directly linked to environmental conditions.

Gorris highlighted that both climate change and resulting human health impacts are national security issues.

Jennifer R. Head from the University of California, Berkeley, described environmental factors that affect the incidence of Valley fever in California. The highest incidence is detected in the San Joaquin Valley, which has a dry and hot climate. However, in the past years, the incidence is increasing most in areas that are not uniformly hot and dry. These increases in incidence come amid unprecedented megadroughts, she explained. Comparing reported cases with environmental conditions suggests that fewer cases are associated with recent rainfall (within the preceding 1–4 months). Increased rainfall in dry counties was associated with especially increased incidence. Hot and dry conditions immediately before exposure were found to promote the incidence, with cooler counties being especially sensitive to heat. Drought and consecutive dry years may immediately suppress incidence but ultimately enhance incidence in the following years. Incidence is increasing most rapidly in wetter and cooler counties, where it is very sensitive to temperature variation, with the largest increases seen following drought. The frequency and severity of droughts are expected to increase with climate change and increasing aridity and greater swings in climate extremes may lead to *Coccidioides* expansion in wetter, cooler areas, Head explained.

#### EXPOSURE TO VALLEY FEVER

Dave Engelthaler from TGen emphasized that exposure risk to *Coccidioides* is complicated. Severe weather events, climate, and human factors may influence the abundance of arthroconidia in the air, which can drive case increases. CocciWatch is a system to detect *Coccidioides* in air samples by use of filter collections. This system provides evidence that *Coccidioides* distribution is not uniform, Engelthaler explained. Though hot spots exist, detection can vary even within the same site depending on time periods. Studies from this system suggest that there is no difference in prevalence between days with and without reported dust storms, but a positive correlation was detected with temperature and wind speed. Wind can move *Coccidioides* and result in dispersed cases but may not result in dispersed ecology. Distinct

phylogeography belies continual wind-driven dispersal. As mentioned, climate change can make conditions more favorable for growth and transmission. However, Engelthaler suggested, it cannot disperse the pathogen. Therefore, Engelthaler hypothesized that humans and animals are the likely long-range dispersal vectors.

Anastasia Litvintseva from the Centers for Disease Control and Prevention further discussed environmental surveillance of *Coccidioides*. In filtered air samples, they found that there is a “patchy” distribution of arthroconidia in the air, and local conditions likely control the prevalence. Air monitoring can be informative for addressing specific questions and testing hypotheses, although results are site-specific, Litvintseva stated. Sampling can be used to better understand the geographic distribution, aiding in monitoring the emergence of *Coccidioides* in new areas due to climate change. Litvintseva remarked that it can also be used to identify potential hot spots (for targeted vaccination, once vaccines are available), and to identify human activities that release arthroconidia in the air, to better understand and mitigate occupational risks.

Daniel Kollath from Northern Arizona University further discussed environmental surveillance in the Phoenix, Arizona, area. Traditional soil sampling is usually taken at a single time point at different locations, making it difficult to examine seasonality patterns and shifts in soil chemistry and in microbial communities. Kollath stated that to better understand the ecology, animals (possible reservoirs, burrows, lung community), dust (dispersal, long and local distance), and soil (microbial ecology, temporal sampling) need to be assessed. The researchers performed a temporal analysis, with a monthly sampling of soil, in targeted and random locations to evaluate the physical and chemical properties of the soil and the effects of climate fluctuations. Air sampling was done every six days. The diversity and abundance of rodents were assessed at positive sites in the Phoenix, Arizona, metro area. Soil sampling targeted burrows and random locations every 5 meters in non-burrow areas. The results suggested that 73 percent of sites were positive, as well as 13 of 14 burrows. Ecological restoration may help limit the spread as the biological soil crust contains

a consortium of different organisms, stabilizes soil, and inhibits the spread of *Coccidioides* spp., said Kollath. In this study, none of the 60 biocrust plots surveyed tested positive for *Coccidioides* spp. This study is ongoing for a total of three years, Kollath said.

Marcus Teixeira from the Northern Arizona University and the University of Brasilia discussed the prevalence of coccidioidomycosis in Brazil, where it is detected mostly in northeast Brazil. A common host for *Coccidioides* in this area is the armadillo. Infections in both humans and dogs have been found to be associated with armadillo hunting; 91 percent of human patients reported this activity. Teixeira and colleagues performed the largest case series analysis outside North America. Valley fever mostly affected males, which may be due to environmental exposures. Other risk factors were manioc (cassava) harvest and other soil-disrupting professions. Genotyping revealed differences with species found in Arizona, but there was similarity with species found in Texas and Mexico.

#### PEOPLE AT RISK FOR INFECTION

Shawnell Damon from Indian Health Services discussed surveillance of Valley fever in the Navajo Nation. Incidence was approximately four times higher for non-Hispanic American Indian or Alaska Native people and almost three times higher for Hispanic or Latino people than for non-Hispanic White people in Arizona in 2020. Therefore, she said, prevention through education is essential, as are improved surveillance and public health research on the geographic spread on reservations. Damon pointed out that state and national data often do not reflect American Indians in demographics, as race is often simply listed as “other.” Damon also highlighted that comorbidities such as obesity, asthma, and diabetes are higher among American Indian communities than White communities. Damon also noted that protective and resiliency factors within these communities include community support, connection with family, and connection with the earth. Damon suggested that prevention and coccidioidomycosis testing can be improved through culturally tailored public health responses and said it is essential that culturally

congruent interventions are considered for these populations.

Kimberley Lucas from the California Correctional Health Care Services (CCHCS) discussed Valley fever epidemiology among California state prison system residents. Ten state prisons, including Pleasant Valley State Prison (PVSP) and Avenal State Prison (ASP), are in highly endemic areas of California. To reduce the impact of Valley fever in these prisons, CCHCS assessed a range of interventions over the years, including medical and demographic restrictions for individuals at higher risk of severe disease and environmental mitigation, Lucas stated. In 2007, despite medically restricting residents with high clinical risk (e.g., immunosuppressed) from placement in any endemic area prison, high rates of Valley fever persisted during the following peak in California (2010–2011). In 2011–2013, PVSP and ASP applied a soil-stabilizing emulsion to control dust and implemented indoor air quality improvements. In 2013, based on findings from a CCHCS assessment of Valley fever rates and risk factors for infection and severe disease at PVSP and ASP, additional medical restrictions were implemented for Black and Filipino residents and those diagnosed with diabetes mellitus in these two prisons. During 2016 (the next peak year in California), Valley fever rates in PVSP and ASP were reduced by about half compared with 2011, while the rates in the other eight endemic area prisons were unchanged. In 2015 CCHCS initiated a *Coccidioides* skin test program and medically restricted residents with negative test results from being placed at PVSP and ASP. However, low skin-test acceptance has likely reduced the impact relative to the clinical and demographic restrictions, Lucas stated. These interventions appear to have substantially decreased Valley fever rates at PVSP and ASP and eliminated disparities in infection, but rates remain orders of magnitude higher than in the surrounding communities, added Lucas.

Marie A. de Perio from the National Institute for Occupational Safety and Health and the Centers for Disease Control and Prevention provided an overview of the occupational risk of Valley fever. It is an important occupational infectious disease, leading to morbidity, missed work time, and health care costs, de Perio stated.

A review of Valley fever outbreaks from 1940 to 2015 revealed that more than half of reported Valley fever cases resulted from occupational exposure (Freedman et al., 2018). People who work outdoors in endemic areas and disrupt soil or work in dusty or windy conditions are at increased risk of infection, she said. Some examples of such occupational groups include workers constructing solar farms, employees of state prisons in California, wildland firefighters, agricultural workers (in particular, work related to root and bulb vegetable crops), and military personnel. Mitigation is especially challenging because some protective measures are not always feasible (i.e., use of respirators) or have unknown effectiveness (i.e., use of soil stabilizers and other environmental mitigation strategies). Considering occupational risk factors and controlling exposures among workers according to the hierarchy of controls, such as implementing dust suppression methods (wetting soil, using soil binders, etc.), can help prevent disease transmission in the workplace, she said. De Perio said that training employees, tracking and reporting illnesses, and identifying criteria by which to suspend work under certain conditions may also decrease spread. Knowledge gaps include understanding the occupational burden of Valley fever, the role of air and soil sampling in workplaces, and the effectiveness of interventions to minimize exposures, she added.

#### **GENOMIC CHARACTERISTICS OF COCCIDIOIDES SPP.**

Bridget Barker from Northern Arizona University discussed the ecology and evolution of *Coccidioides immitis* and *Coccidioides posadasii*. There is a strong biogeographic link between patterns of isolates from different regions, with *C. immitis* mostly detected in the region from California to Baja, Mexico, and *C. posadasii* in the region encompassing the U.S. Southwest, Mexico, Brazil, and Argentina. Barker explained that understanding genetic variation allows the assessment of pathogenicity differences between species that may require different treatment strategies. In terms of epidemiology, there may be differences in interactions or outbreak patterns. Barker's team found that the genome has lost plant-associated gene families over time, while it has expanded genes related to keratin degradation, which suggests close interaction with animals. Given that infection results from inhaling arthroconidia from the soil, dust,

or air, understanding of the ecology and environmental reservoir is critical, said Barker. There is no evidence of transmission from an infected human host. Data on the environmental niche are limited, and this limits climate modeling and predictive ability. Regions colonized with *Coccidioides* are generally hot and dry and have alkaline soil occupied by several endemic species. Burrows often represent point sources of infection in outbreaks. Barker further discussed the small mammal reservoir hypothesis and the life cycle of *Coccidioides* species, as detailed in John Taylor's talk. Climate affects not only the soil but also the abundance of small mammals. Long-term monitoring of positive sites showed that these stayed positive for decades and that the majority of isolates retrieved from a single site are clones. Patient isolates, on the other hand, are mostly different genotypes. It remains unclear if genotypes change over time and how, said Barker.

Steven M. Holland from the National Institute of Allergy and Infectious Diseases (NIAID) at the National Institutes of Health (NIH) discussed gene and environment interactions. Some risk factors for disseminated coccidioidomycosis in the United States are pregnancy, HIV infection, and immunosuppression, as well as mutations in genes associated with the IL-12/IFN- $\gamma$  pathway. Collectively, previous research had only identified eight mutations when looking for rare Mendelian variants using whole exome sequencing, Holland explained. But since this is a virulent, geographically limited disease that affects healthy people, Holland suggested that rare variants might not be the right filter for research into genetic sensitivity to infection. Therefore, patients with disseminated disease were assessed for more common mutations. Some defects were found in cellular Dectin-1, which binds fungal  $\beta$ -D-glucan, and variants like Dectin-1 p.Y238\* are impaired in  $\beta$ -glucan induced signaling pathways. Some other mutations, such as PLC $\gamma$ 2 p.R268W, and DUOX1 and DUOXA1 variants, were also found in subsets of patients. These mutations affect pathways involved in response to  $\beta$ -glucan, including TNF $\alpha$  and H<sub>2</sub>O<sub>2</sub> production. Therefore, many relatively common variants in disseminated *Coccidioides* are associated with early fungal sensing and antifungal responses.

Jason Stajich from the University of California, Riverside, discussed genomic resources and comparative analyses. The goal of his work is to build resources to enable investigations of the biology and evolution of *Coccidioides* spp. to allow investigation into the genetic basis of their unique biology. Stajich's research is focused on investigating genomic stability among different fungal isolates and species, genetic manipulations, gene expression and developmental stage comparisons, understanding of metabolism pathways, and antifungal susceptibility. This research can also support work toward vaccine production. Various resources are available for genomics research from Sanger sequencing and Illumina sequencing to RNA sequencing profiling and microarrays and reference genomes with long read sequences. The *Coccidioides* genome is about 30 megabases in size and contains approximately 10,000 genes. Sequencing studies have revealed a diversity of transposable elements within *Coccidioides* genomes, Stajich explained.

Anita Sil described her work with colleagues from the University of California, San Francisco, investigating the transcriptional profiling of *Coccidioides* during development from arthroconidia to either spherules or hyphae. Dramatic transcriptional shifts occur during these transitions. These transcriptional profiles of spherules and hyphae are partially dependent on the transcription factor Ryp1. Mutations in this gene are avirulent in the mouse model of infection (Mandel et al., 2022). SOWgp is a spherule outer wall protein specific to *Coccidioides*. Mutants that lack SOWgp show decreased virulence (Hung et al., 2002), and SOWgp levels in spherules are Ryp1-dependent (Mandel et al., 2022). Sil and colleagues also evaluated interactions between murine bone-marrow-derived macrophages and *Coccidioides* using an *in vitro* macrophage model system. They found that macrophages stimulate *Coccidioides* spherulation, a process that is contact-dependent.

#### CHALLENGES WITH DIAGNOSTICS FOR VALLEY FEVER

Fariba Donovan from the University of Arizona College of Medicine and the Valley Fever Center for Excellence discussed current diagnostic challenges for Valley fever. Donovan stated that raising awareness of the disease



is key to an early diagnosis, noting that 42% of Valley fever diagnoses are delayed by more than 30 days. Furthermore, 40 percent of clinicians in Arizona are not confident in how to treat Valley fever. Banner Health and the University of Arizona have developed a tool kit to improve Valley fever recognition and management among physicians. Additionally, the development of rapid point-of-care testing with high sensitivity and specificity is critical for early diagnosis, said Donovan. Accuracy of currently available diagnostic tests is variable. A novel lateral flow assay developed by IMMY and tested in a prospective study by Donovan and colleagues (2021) is promising, with speed and high specificity, but the test required improved sensitivity for point-of-care use, she said.

Amanda Burnham-Marusich from DxDiscovery and the University of Nevada, Reno, also emphasized that besides awareness, better rapid diagnostic tools are urgently needed. The major factor that delays diagnosis with the currently available tools is the turnaround time between specimen collection and test result. Antigen-detection lateral flow immunoassay is a technology that might be useful to enhance Valley fever diagnosis. This diagnostic assay has been developed to use urine or serum to detect *Coccidioides* spp. mannan. Developments are under way to improve its sensitivity. With developing new technologies, a balance needs to be achieved between enhancing an assay's sensitivity and maintaining the assay's point-of-care nature and accessibility. In this case, the clinical needs will determine feasible strategies. Burnham-Marusich concluded that considerations for future research into diagnostic tools are whether the use of a reader would be acceptable (costs plus electricity requirements) and at what stage of the disease the assay can produce a positive result (how big is the clinical utility window).

Ian McHardy from Scripps Health discussed diagnostics for coccidioid meningitis. This is currently assessed by clinical presentation and analysis of the cerebrospinal fluid (CSF), including detection of CSF anti-coccidioid complement-fixing antibodies and culture/microscopy, both of which have poor sensitivity. The consequences of

false negatives and positives are serious in this disease. A false negative result can be fatal if meningitis goes untreated, and a false positive would lead to lifelong antifungal treatment with drug toxicity affecting quality of life. McHardy's research is focused on identifying host metabolomic changes associated with the progression of coccidioid meningitis to develop improved diagnostics. McHardy and colleagues found sex differences in the susceptibility to coccidioid meningitis, which could be important for the development of diagnostic tools.

Another technology that is gaining interest for diagnostic purposes is breath testing. Research by Heather D. Bean's team from Arizona State University showed that the two *Coccidioides* species do not have a species-specific volatile organic compounds (VOC) breath profile, which makes a universal breath test for Valley fever feasible. Furthermore, VOCs can differentiate fungal from bacterial pneumonia, potentially reducing improper diagnosis and unnecessary antibiotic use. Valley fever VOCs were also found to correlate with the immune response and may correlate to disease severity. This type of testing may allow for a reduction in improper treatment and improve assessment of disease stage, Bean stated.

#### **CURRENT TREATMENT OPTIONS AND DEVELOPMENT OF NEW THERAPEUTICS**

George R. Thompson from the University of California, Davis Medical Center discussed complications in treating Valley fever, including a lack of targeted antifungal therapies, toxicity of existing therapies, and challenges regarding the development of new therapies. In primary pulmonary infection, the question remains whether treatment affects outcomes, as illness in most of these patients will self-resolve and treatment may not change the duration of symptoms and cannot prevent dissemination. However, patients who are immunosuppressed; have diabetes mellitus, cardiovascular disease, or exceptionally severe primary disease; or are pregnant, Filipino, or African American should always be treated, Thompson said. Complicated disease, on the other hand, requires long courses of therapy for all patients. Treatment durations of many years are necessary in most severe cases and

are associated with toxicity and affect quality of life. Furthermore, therapy resistance is emerging, suggesting more treatment options are urgently needed, Thompson remarked.

John H. Rex from F2G discussed some of the hurdles in the development of new therapies. Developing a new drug for coccidioidomycosis has proven very challenging. Some basic requirements that are warranted for such drugs include oral administration, safety data from a long duration of dosing, and substantial drug supply that is available to support both animal safety studies and clinical studies. There are several feasibility challenges for randomized control trials (RCT) for new anti-*Coccidioides* therapies. There are no easy trial populations for an RCT, which means that phase 2 dose-finding studies are difficult to conduct. There are no standard comparators, and available endpoint tools are limited, as are performance data with those tools. An updated consensus on what is adequate for *Coccidioides* and other invasive fungal infections is needed, Rex stated. Unfortunately, there is no easy fix for these challenges. It will be important to establish baseline data to determine a benefit-risk score for rare infections. Rex discussed benefits and disadvantages of various trial designs as well as the best patient population to study in such trials.

John N. Galgiani from the University of Arizona and the Valley Fever Center for Excellence also addressed the challenges emerging for the development of drugs and vaccines for coccidioidomycosis. Galgiani discussed various scoring systems to assess the efficacy of new drugs. All drugs currently used for *Coccidioides* were originally developed for other fungal diseases. Therefore, the established path for developing new treatments for *Coccidioides* is to obtain Food and Drug Administration (FDA) approval for another indication. A challenge for performing RCTs is the lack of FDA-approved endpoints for disseminated and chronic pulmonary infections. Furthermore, since there is no FDA-approved treatment that works well, non-inferiority designs are not possible. For primary *Coccidioides* infection, no previous studies have been completed, and the only feasible endpoint is a reduction in the length of illness, as preventing

complications would require a very large study population. Many symptoms are immunologic responses triggered by infection, and the effect of antifungals on their resolution is uncertain. Finally, because the disease is often diagnosed late, the opportunity to determine a therapeutic effect might be missed.

Thomas F. Patterson from the University of Texas Health Science Center discussed new potential targets and compounds under early and more advanced stages of development. This includes novel methods of delivery for old drugs, new uses for existing compounds, new agents in currently used classes, and new compounds with novel mechanisms of action. Patterson described recent positive experiences treating patients with disseminated coccidioidomycosis with olorofim, a drug that is currently in phase 2 clinical trials. He also described rezafungin, a novel echinocandin antifungal, which expresses improved safety profiles and is in phase 2 and phase 3 clinical trials for use against *Candida auris* and *Aspergillus* spp.

#### VACCINE DEVELOPMENT

With limited therapeutic options, a vaccine to prevent infection could significantly reduce the burden of Valley fever. John Galgiani stated that there is a good rationale for a vaccine, as patients are presumed to have lifelong immunity after infection. For U.S. Southwest residents and tourists, a vaccine could prevent about 50,000 primary cases and about 750 disseminated infections per year, with a potential cost reduction of \$1.5 billion, he said (Grizzle et al., 2021; Wilson et al., 2019). It would also prevent unnecessary antibiotic use from misdiagnosed cases. However, similar to therapeutics RCTs, questions on what populations to study and what endpoints to assess need to be addressed for vaccine RCTs, according to Galgiani.

Royce H. Johnson from Kern Medical discussed a previous attempt to develop a vaccine for Valley fever. From the 1960s to the 1990s, a whole formaldehyde-killed spherule (FKS) vaccine was developed and showed promise in mouse models. Human studies involved a whole-cell vaccine. This vaccine failed because of dose restrictions because of its toxicity and other side effects, Johnson explained. Furthermore, the study was small and mostly

included lower-risk populations. Ultimately, the FKS vaccine was not found to be effective in preventing Valley fever in humans. Johnson noted that more recent attempts to develop other vaccines have shown that most target antigens have not progressed beyond research in mouse models. Key considerations for future phase 3 trials are sample size, measurement of previous immunity, and recruitment of representative samples, said Johnson.

Some of the more recent developments in vaccines for Valley fever include the successful development of a live attenuated vaccine candidate for dogs. Lisa Shubitz from the University of Arizona explained that the vaccine strain of *C. posadasii*, featuring a deletion of the *CPS1* gene, was found to be avirulent in mice and protects mice from infection. The *CPS1* gene is critical for spherulation and propagation in this parasitic phase. A study was started to develop this dog vaccine as a step toward developing a vaccine for humans. The vaccine had few adverse events in dogs, causing no systemic effects and inducing only transient mild to moderate injection-site swelling that resolved two weeks post-booster. Prime and booster dosing generated good protection against infection independent of *Coccidioides* exposure levels. The vaccine is in the process of becoming licensed, Shubitz said.

Thomas P. Monath from Crozet BioPharma discussed the further development of this canine  $\Delta$ *CPS1* vaccine toward a human vaccine. At the moment, funding and policy, rather than technical risk for the human vaccine, remain the principal challenges. Monath explained that with the development of the dog vaccine, major elements of Good Manufacturing Practice (GMP) manufacturing and analytics were already addressed. The human vaccine would require some further developments, including additional downstream purification to achieve a stable, liquid frozen drug product. These needs were discussed with a contract development and manufacturing company and no difficulties were envisioned. Some regulatory considerations for the human clinical trials for this vaccine include efficiency in collecting clinical data, diagnostic precision, the regulatory requirement for more than one trial, addressing whether to eliminate the population that tests positive on the skin test from

the trial to focus on the susceptible population, and whether to research specific populations at the highest risk, he explained. He stated that financing of such trials is estimated to cost \$200–300 million. The market for this vaccine would be relatively small and regional, but Monath believes it is a potentially profitable market. However, public funding and incentives are required to initiate such RCTs. Private investors are expected to follow with the advance of clinical development to further fund the clinical development. Overall, Monath stated that the advancement of a human live attenuated vaccine would be feasible, effective, and beneficial.

Other options for coccidioidomycosis vaccines are in early-stage development. Chiung-Yu Hung from the University of Texas discussed work developing a subunit vaccine. Th1- and Th17-mediated immune responses are essential for immunity against pulmonary *Coccidioides* infection. Antigens were identified that were expressed in human infection and would stimulate and activate CD4<sup>+</sup> T cells. A subunit vaccine was created using T-cell epitopes and an adjuvant and delivery system that can stimulate Th1 and Th17 immunity. The *Coccidioides* polypeptide antigen (rCpa1) was selected for the vaccine, with glucan chitin particle (GCP) as the adjuvant. This GCP-rCpa1 vaccine showed comparable protective efficacy to a live attenuated vaccine in mice. A human study to assess CD4<sup>+</sup> T-cell responses to rCpa1 found higher levels of these responses in recovered patients than in healthy donors. Research is ongoing to discover additional antigen epitopes that can be used for optimization of vaccine antigen design and evaluate immune correlates, vaccine adjuvants, and preclinical *ex vivo* T-cell recall assays, Hung stated. Current research initiatives aim to bridge to clinical trials, GMP production of vaccine components, and scale up.

Deborah Fuller from the University of Washington discussed options for nucleic acid vaccines for Valley fever. Nucleic acid vaccines offer many features that align with what may be needed for an effective Valley fever vaccine, she explained: they can induce Th1/Th17 responses and mucosal immunity, enable multi-antigen vaccine composition, are easy to manufacture and scale up, are amenable to needle-free or self-administration,

and have a track record of safety and efficacy in humans. Nucleic acid vaccines also offer a valuable tool for immunogen discovery. One caveat is that viral antigens expressed by nucleic acid vaccines closely mimic viral infections, and with fungal antigens, this may present a new challenge. Fuller described the self-amplifying RNA vaccine platform that her team is working on (repRNA/LION), which is distinct from mRNA vaccines as it produces more of the protein antigen, is self-adjuvanting, and elicits a stronger immune response at a low dose. Fuller's lab is also developing an animal model in nonhuman primates (pigtail macaques, *M. nemestrina*). It is the closest available model to humans, as these macaques are vulnerable to the same disease and exhibit similar clinical presentation as humans. Therefore, this model may enable studying stages of infection that are not possible or challenging in humans. This may help gain a better understanding of how *Coccidioides* causes disease and immune mechanisms of protection.

#### OUTLOOK AND AVAILABLE SUPPORT FOR RESEARCH ENDEAVORS

Various initiatives are under way or proposed to aid research into medical countermeasures. Dona Love from the NIAID at the NIH presented an overview of the NIH research grants portfolio. The NIAID utilized special program announcements and requests for applications to increase applications and grants and established a strategic plan for research to develop a coccidioidomycosis vaccine, Love said. The institute published a request for information to solicit community comments structured around three areas of research considered vital to develop a vaccine: understanding of pathogenesis and host responses, developing tools and resources to support research, and advancing strategies to treat and prevent the disease. In response to this, a 10-year (2022–2032) benchmark overview toward a Valley fever vaccine was developed, which aims for phase 1 and phase 2 clinical trials by 2032.

Finally, Katherine Phillips, health legislative assistant from the office of Senator Mark Kelly of Arizona, discussed the Finding Orphan-Disease Remedies with Antifungal Research and Development (FORWARD) Act, which is aimed at progressing vaccine development

for fungal diseases by funding research over the course of five years. The act would establish a fungal diseases working group and facilitate coordination with NIAID, allow for fast-tracked review of drugs for coccidioidomycosis treatment, and require the Biomedical Advanced Research and Development Authority to seek projects focused on antibacterial and antifungal products. If approved, this act would open extra funding opportunities for diagnostic, treatment, and vaccine development for Valley fever, Phillips stated.

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**REVIEWERS** To ensure that it meets institutional standards for quality and objectivity, this Proceedings of a Workshop—in Brief was reviewed by **MANISH BUTTE**, University of California, Los Angeles, and **SINEM BEYHAN**, J Craig Venter Institute. **LESLIE SIM**, National Academies of Sciences, Engineering, and Medicine, served as the review coordinator.

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**SPONSORS** This workshop was supported by Anivive Lifesciences, Centers for Disease Control and Prevention, CURE Drug Repurposing Collaboratory, F2G, Fortress, MiraVista Diagnostics, Mycovia Pharmaceuticals, Nielsen BioSciences, University of California–San Francisco, and Valley Fever Americas Foundation Board.

For additional information regarding the workshop, visit <https://www.nationalacademies.org/our-work/impact-and-control-of-valley-fever-a-workshop>.

Suggested citation: National Academies of Sciences, Engineering, and Medicine. 2023. *Impact and control of valley fever: Proceedings of a workshop—in brief*. Washington, DC: The National Academies Press. <https://doi.org/10.17226/26928>.