# Valley Fever: Where are we now?

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## Abstract

**Introduction:**
Coccidiomycosis, also known as Valley fever, is a respiratory fungal infection that enters the host through inhalation and then resides in the lungs. Coccidiomycosis can be caused by two distinct fungal species *Coccidioides immitis* (*C. immitis*) and *Coccidioides posadasii* (*C. posadasii*). Infection can be spread by the soil form of the fungus, the arthroconidia, entering the host, and higher concentrations of arthroconidia have been linked to more severe cases of disease. After exposure to the fungal pathogen, 60% of individuals will be asymptomatic, while the other 40% will have symptoms. Once a patient has been diagnosed with Valley fever, they may go on fungal therapy for a certain time depending on the severity of their infection. Coccidiomycosis is infectious but not contagious from patient to patient. Patients can develop disseminated coccidioidomycosis, which occurs when the fungal infection no longer just resides in the lungs; disseminated coccidioidomycosis has been linked to weak innate immune responses.

**Relevance:**
Valley fever has been on the rise in endemic and non-endemic areas due to climate change, social, and economical changes that have cause the expansion of coccidiomycosis to other regions. Although coccidiomycosis is not statistically a fatal disease, it is a life lasting disease that can affect many, especially those in or near endemic areas. This project has allowed me to educate myself about Valley fever with the intention to provide accurate information to the public in both English and Spanish, focusing on those residing in the Central Valley or endemic areas. Through the Student Success Internship, I was able to work with Dr. Katrina Hoyer and her lab, exposing myself to scientific researching focusing on coccidioidomycosis, and immune responses. It is important for the public to be informed about coccidioidomycosis, especially those in endemic aeras such as the San Joaquin Valley, as they are at a higher risk of exposure to Valley fever.

## Valley Fever: Disease and Symptoms

Fig. 1

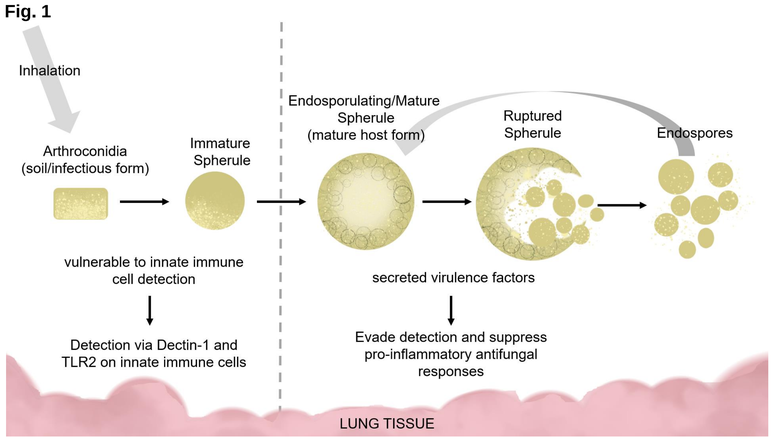


**Figure 1. *Coccidioides* life cycle in host lung.** Early infection: *Coccidioides* is vulnerable to immune detection due to its smaller size (2–5 μM) and *Coccidioides*-antigen is detected via Dectin-1 (cell receptor involved in immune response against fungal pathogens) and TLR2 (a membrane protein receptor, which aids in the identification of fungi) on innate immune cells. Later infection: As *Coccidioides* sporulates, immature spherule to mature spherule, it releases virulence factors that shields it from immune detection. Spherules also release virulence factors that influence host tissues, suppressing inflammation via an unknown mechanism, contributing to immune suppression.

**Valley Fever symptoms:**
- Fatigue
- Cough
- shortness of breath
- Headaches
- Night sweats
- Muscle or joint pain

**Disseminated coccidioidomycosis symptoms:**
- Nodules on other parts of body
- Skin lesions
- Painful lesion in the bones
- Swollen joints
- Meningitis – inflammation of the fluid and membranes surrounding brain and spinal cord

**Symptoms associated with chronic coccidioidomycosis**:
- Weight loss
- Chest pain
- Nodules in the lungs
- Fever

## Epidemiology

Coccidiomycosis is endemic to regions of Southwestern United States, Mexico, Central and South America. Epidemiological research has shown that the United States has at least 150,000 new cases in the United States related to coccidiomycosis. In the past 15 years, there has seen an increase of coccidioidomycosis in California, a rise of 25,000 cases. The 2016 annual rate of infection in Arizona is 89.3/100,000 and 13.7/1000,000 in California. Climate change and population increases in certain endemic areas have been linked to the cause of increasing infection rates of coccidiomycosis in endemic region and nearby aeras. Some of California's endemic regions include Central valley, Kern County, and Central Coast, as 70% of Californian Valley fever cases come from these regions.

**Who it impacts:**
- African Americans & Filipinos are a higher risk of developing disseminated coccidioidomycosis
- The elderly have higher risk of developing disseminated coccidiomycosis compared to children
- People working in the outdoors near soil and dust such in endemic areas such as military personnel, construction workers, farm workers
- People with immunosuppression, or diseases that impacts T-Cells production/function

Recent local and state efforts have led to the development of education tools to teach K-12 children the signs of Valley Fever within endemic areas. These resources are in both English, Spanish, and Tagalog to span the broad diversity of communities the disease impacts.

**K-12 Learning Resources from LA County:**
http://publichealth.lacounty.gov/acd/Diseases/Cocci.htm

The link above has youth-friendly presentations, study guides, posters, and in-class activities that can be used to help educate children about the fungus that causes Valley fever and the disease symptoms.

Such material can be adapted for the Central Valley community as well!

## Immunity to VF: What do we know?

Fig. 2

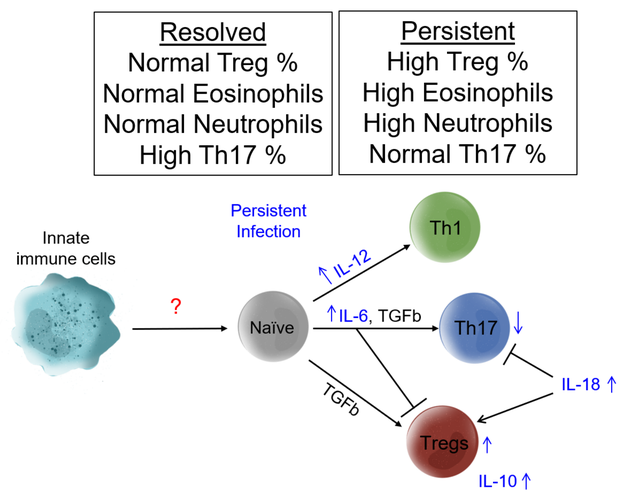


**Figure 2. Hoyer Lab pediatric study reveals immune differences between patients who resolve their infections versus patients who have persistent, chronic disease.** The Hoyer Lab analyzed the peripheral blood from 34 pediatric patients (2-18 years of age) in various disease resolution states were analyzed for immune cell population frequency and cytokine levels. Statistical analysis revealed a relationship between %CD4+ Treg (T-cells which regulate or suppresses immune response) and disease outcome. Tregs (regulatory T cells), as a parameter, was able to separate patients who had resolved their disease versus those that developed chronic disease. Cytokine (immune cell communication molecules) levels analysis of patient blood also revealed an elevated concentration of key effector cytokines associated with Treg function (IL-6 proinflammatory cytokine, IL-10 anti-inflammatory cytokine) and innate immune cell function (IL-18 proinflammatory cytokine, IL-12 proinflammatory cytokine, regulates T-cells and Natural killer cells).

*(Dan Davini, Fouzia Naeem, Aron Phong, Mufadhal Al-Kuhlani, Kristen M. Valentine, James McCarty, David M. Ojcius, David M. Gravano, Katrina K. Hoyer. J Allergy Clin Immunol. 2018 Dec;142(6):1971-1974 )*

## Vaccine and Genetic Susceptibility

**Vaccine:**

Coccidiomycosis is considered a neglected disease since the 60% of infected are asymptomatic and 40% result in symptoms. Due to the work of countless advocates, clinicians, and researchers, the need for a vaccine is now considered urgent and vital. Vaccines help patients develop immune memory to fight off infections. Fungal pathogens such as *Coccidioides* are difficult to develop vaccines for due to the many life cycle forms, which helps them evade immune detection.

**Mouse Vaccine Studies:**

- Inactivated vaccine refers to a killed pathogen used to prime the immune response. Formalin-killed spherules were vaccinated to mice and was successful in providing protection in mice upon secondary challenge with live, virulent *Coccidioides*.
- Heat-killed yeasts were given to mice 21,14,7 days before being given *Coccidioides* spores. This led to 50-70% survival in the first 28 days, while the nonvaccinated group had 90% death within the first 16-18 days.
- A possible live, attenuated vaccine was created by genetically modifying a strain of *C. posadasii* by targeting CTS2 and CTS3 (disrupting chitinase genes, which prevents Coccidioides from reproducing within the host). The vaccine caused mice to have a decrease in proinflammatory cytokines (immune cell communication molecules), and reduced tissue damage.
- Current vaccine research has concluded that for a successful vaccine to be created it must increase CD4+T cell responses (which aid in immune response by stimulating other cells) since their immunity is essential for protection. Vaccines must also create activation of Th1(stimulates cellular immune response against bacteria, viruses), Th2 (stimulates immune response against extracellular parasite), and Th17 (stimulates immune responses against fungal and extracellular pathogens) responses.

This vaccine seems to be promising, easy to produce, and predicted to be safe for humans. There is current work looking into adapting the attenuated strains of *Coccidioides* for human vaccination.

**Genetic susceptibility as shown in Case Study Examples:**

- Mutation resulting in short isoforms in cell signaling receptors increase susceptibility. Short isoforms cannot respond to cytokines due to lack of signal domains for effective immune cell communication.
- Mutations in the CARD9 gene have been linked to high susceptibility to fungal infections. The gene codes for a communication signaling molecule used with Dectin-1 and C-type lectin receptors, two receptors that play a role in helping immune cells recognize fungal pathogens.

## Summary

Valley fever is a fungal infection cause by the inhalation of *C. immitis* or *C. posadasii*, which can be found in the soil of endemic regions, such as the Central Valley. There has been an increase in coccidioidomycosis cases throughout the United States that has been linked to climate change, allowing the pathogen to spread to other regions. Epidemiology studies have shown the increase of coccidioidomycosis exposure and tracked the number of cases in endemic regions, in hopes of increasing and improving diagnosis techniques for Valley fever. Although most coccidioidomycosis cases are asymptomatic, disseminated and chronic cases have been linked to early immune suppression in patients. Current research highlights the need for a vaccine. Our communities, especially those located or near the endemic areas should be educated and have access to resources regarding Valley fever, especially those who are working with or near soil, as many my lack health insurance or coverage and fungal therapy and treatment for Valley fever can be expensive.

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