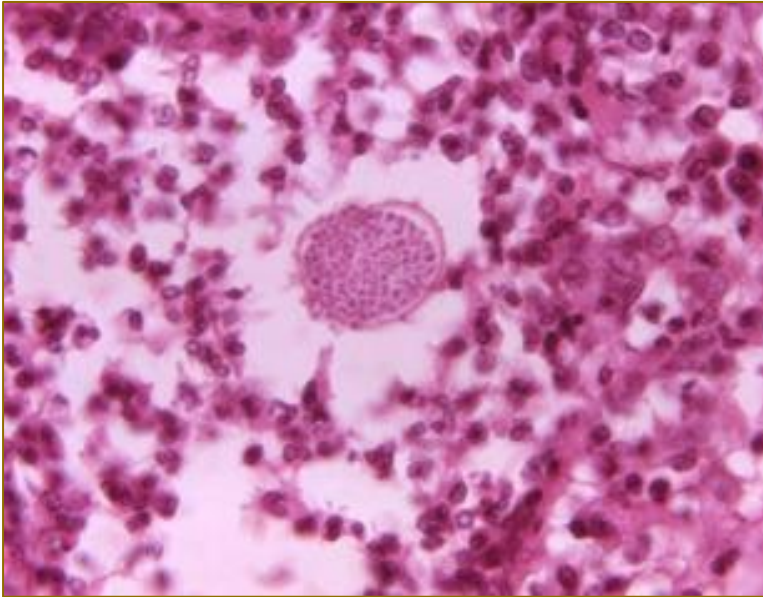




Credit: CDC/Dr. Brodsky

NIAID STRATEGIC PLAN FOR RESEARCH TO DEVELOP A VALLEY FEVER VACCINE

NIAID Valley Fever
Research Working
Group

September 2022



National Institute of
Allergy and
Infectious Diseases

Contents

Executive Summary	2
Introduction.....	4
Strategic Priority 1: Address Gaps in <i>Coccidioides</i> Basic Research to Support the Development of a Vaccine	6
Objective 1.1 Evaluate Factors Contributing to <i>Coccidioides</i> Geographic Spread.....	6
Objective 1.2 Improve Understanding of <i>Coccidioides</i> Biology and Life Cycle	7
Objective 1.3 Characterize Host Responses to Infection and Disease.....	7
Objective 1.4 Characterize Virulence Factors	8
Strategic Priority 2: Develop Tools and Resources to Support <i>Coccidioides</i> Vaccine Research..	9
Objective 2.1: Advance Development of Biomarkers and Rapid Point-of-care Diagnostics	10
Objective 2.2: Develop Cell Culture and Animal Models that Reflect Human Disease	11
Objective 2.3: Leverage and Expand Clinical Capacity to Promote Collaboration	11
Strategic Priority 3: Develop and Advance Vaccines to Prevent Coccidioidomycosis.....	12
Objective 3.1: Support and Advance Rational Design of Vaccines for Valley fever.....	12
Objective 3.2: Test Vaccine Candidates in All Populations	13
Conclusion	13
Appendix 1. Valley Fever Strategic Plan Working Group Members.....	15
Appendix 2. Analysis of Public Comments to Request for Information (RFI)	16
Appendix 3. Vaccine Development Benchmarks, Criteria, and Market Analysis for a Valley Fever Vaccine.....	18
Appendix 4: NIAID-Supported Valley fever Research Resources	20

Executive Summary

The National Institute of Allergy and Infectious Diseases (NIAID) at the U.S. National Institutes of Health (NIH) is committed to advancing research on Valley fever, including the development of a safe and effective Valley fever vaccine. Valley fever—caused by the *Coccidioides* fungus—is one of the most common endemic fungal infections in the United States, with over [20,003 cases](#) reported in 2019. The *Coccidioides* fungus resides in the soil and its spores can be inhaled by people when the ground is disturbed, resulting in respiratory infection. Symptoms often resolve within a few months, but in some cases the *Coccidioides* fungus can cause severe pneumonia or disseminate to parts of the body beyond the lungs. Severe cases are more common in people who are immunocompromised, pregnant, 60 years of age and older, or members of certain racial and ethnic groups including Black and African Americans, and Asian Americans.

Although Valley fever cases have been traditionally found in the arid regions of the southwestern United States and South America, the discovery of local spread in the Pacific Northwest suggests that changes in weather and climate may be increasing the geographic spread and incidence of *Coccidioides* infection. To date, Valley fever treatment strategies using antifungal drugs remain challenging because of the variability in disease severity and potential host risk factors, both of which impact the type and duration of treatment. More research is needed to identify better treatments for Valley fever. The increasing threat that Valley fever poses to public health underscores the urgent need for the development of safe and effective medical countermeasures

Currently, no vaccine is licensed to prevent Valley fever, despite ongoing research since the 1960s. Because *Coccidioides* infection in people usually provides protective immunity from reinfection, developing a safe and

NIAID Strategic Plan for Research to Develop a Valley fever Vaccine

Mission: Develop a vaccine for Valley fever
Vision: Stop the increasing public health threat due to Valley fever

effective vaccine is generally thought to be feasible and would be expected to provide durable immunity. A safe and effective vaccine against *Coccidioides* infection could protect residents in the affected areas in the United States and other countries.

To protect people against *Coccidioides* infection, the NIAID *Strategic Plan for Research to Develop a Valley Fever Vaccine* reflects the NIAID research priorities for developing a Valley fever vaccine. The plan outlines three strategic priorities to achieve this goal:

- **Strategic Priority 1: Address Gaps in *Coccidioides* Basic Research to Support the Development of a Vaccine** — elucidate epidemiological factors, geographical spread,

and fungal and host factors underlying pathogenesis and host immune response, including correlates of immunity

- **Strategic Priority 2: Develop Tools and Resources to Support *Coccidioides* Vaccine Research**— biomarkers, cell culture and animal models, diagnostics, and clinical research capacity
- **Strategic Priority 3: Develop and Advance Vaccines to Prevent Coccidioidomycosis**— focus on strategies to advance vaccine design, adjuvants, and alternative delivery methods, prioritizing the inclusion of high-risk populations in clinical trial testing

These interdependent activities (Figure 1) will require a concerted effort by the research community and public health stakeholders to develop a safe and effective vaccine for Valley fever for use in at-risk populations. NIAID anticipates that this plan will serve as a basis for such activities as well as future research needed to develop a vaccine for Valley fever.

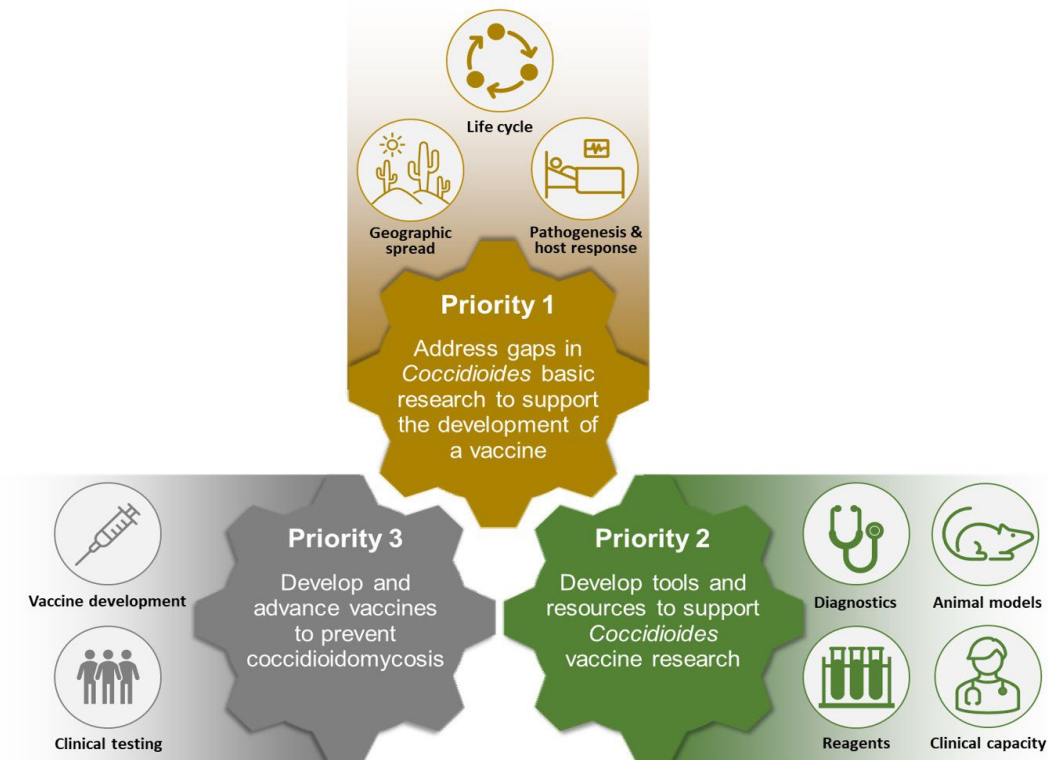


Figure 1: NIAID Strategic Plan to develop a vaccine for Valley fever research priorities. Priority 1: Address gaps in Coccidioides basic research to support the development of a vaccine. Priority 2: Develop tools and resources to support Coccidioides vaccine research. Priority 3: Develop and advance vaccines to prevent coccidioidomycosis.

Introduction

Coccidioidomycosis, more commonly known as Valley fever, is a fungal infection of increasing public health concern in the U.S. Valley fever is most common in the arid regions of the southwestern U.S. and Central and South America and is among the most common endemic mycoses in the United States. Valley fever is caused by the soil-dwelling fungi *Coccidioides immitis* or *Coccidioides posadasii* that establish infection in the lung after inhalation. Although many cases of Valley fever are asymptomatic and self-limiting, approximately 40 percent of infected individuals develop significant flu-like symptoms including cough, fever, chest pain, and fatigue, which can last weeks to months and require antifungal therapy. In some cases, infection can spread to the brain, skin, or bones. Severe disease occurs in approximately one percent of infected individuals, resulting in severe morbidity or death and necessitating life-long antifungal therapy. Approximately 200 coccidioidomycosis-associated deaths were reported each year on average in the United States from 1999 to 2019. While disseminated spread is rare, it is more common among certain racial and ethnic groups including Black and African Americans, Filipinos, people with a weakened immune system, and women during the third trimester of pregnancy. Additionally, rates of Valley fever are usually highest among people aged 60 and older.

Although much progress has been made in understanding the biology of *Coccidioides* as well as the host response to infection, there are still significant gaps in scientific knowledge, molecular tools, and resources that need to be addressed. One of the challenges in research towards the development of a vaccine is the unique dimorphic life cycle of *C. immitis* and *C. posadasii*, which alternates between a saprobic, or soil-dwelling phase, and a spherule/endospore parasitic phase in an animal host (Figure 2). Transition between the saprobic phase and parasitic phases occurs when soil containing *Coccidioides* is disturbed and arthroconidia, or spores, are dispersed. In some cases, arthroconidia return to the ground and re-establish a saprobic life-cycle phase. In other cases, inhalation of arthroconidia by humans or animals supports the transition of the fungus into the parasitic phase. Inhaled arthroconidia undergo cellular changes and numerous rounds of nuclear division in the lungs, leading to the development of larger spherules and the production of numerous endospores, which result in sustained pathology in the host.

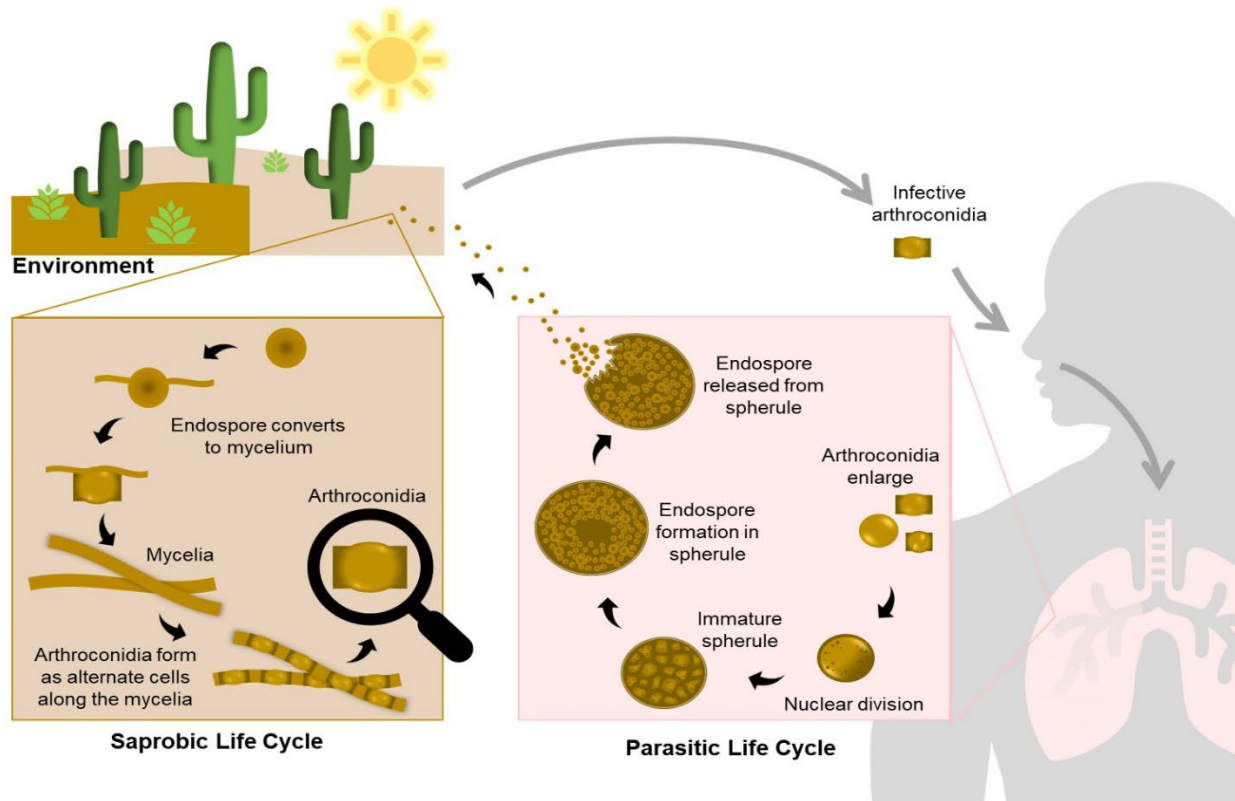


Figure 2: ***Coccidioides* life cycle.** *Coccidioides* have a unique dimorphic life cycle, which alternates between a saprobic (soil-dwelling) phase, and a spherule/endospore parasitic phase in an animal host. Transition between the saprobic phase and parasitic phase occurs when soil containing *Coccidioides* is disturbed and arthroconidia, or spores, are dispersed. In some cases, arthroconidia return to the ground and re-establish a saprobic life-cycle phase. In other cases, inhalation of arthroconidia by humans or animals supports the transition of the fungus into a parasitic phase. Inhaled arthroconidia undergo cellular changes and numerous rounds of nuclear division in the lungs leading to the development of larger spherules and the production of numerous endospores, which can result in disease.

In 2019, the Centers for Disease Control and Prevention (CDC) reported [20,003 cases](#) of Valley fever. However, many patients go undiagnosed or misdiagnosed due to delays in testing, suggesting that this may be an underestimate of cases. Historical trends suggest that the prevalence and geographic spread of Valley fever has steadily increased over the past decade, underscoring the urgency and need for the development of better medical countermeasures. To address these issues and develop the *NIAID Strategic Plan to Develop a Valley Fever Vaccine*, a Valley Fever Working Group consisting of scientific, policy and subject matter experts within NIAID was convened to advance progress in the field where obstacles and significant gaps in scientific knowledge still exist. To seek broad public input, NIAID published a Valley fever Request for Information (RFI), and also targeted community stakeholders, such as Southwestern Native communities. The RFI garnered responses from a variety of organizations which were incorporated into this plan. Leveraging this broad expertise, this plan is organized around three interdependent strategic priorities to advance research towards the development of a Valley fever vaccine: understand *Coccidioides* pathogenesis and host responses, develop

tools and resources to support *Coccidioides* vaccine research, and develop and advance vaccines to prevent Coccidiomycosis.

Strategic Priority 1: Address Gaps in *Coccidioides* Basic Research to Support the Development of a Vaccine

Developing a vaccine for Valley fever will require continued advances in the understanding of the complex molecular and immune mechanisms underlying infection and disease. Improving our understanding of the coccidioides life cycle and geographical spread is essential to understanding transmission and infection and informing the development of countermeasures.

Strategic Priority 1: Address Gaps in *Coccidioides* Basic Research to Support the Development of a Vaccine

1. Evaluate Factors Contributing to *Coccidioides* Geographic Spread
2. Improve Understanding of *Coccidioides* Biology and Life Cycle
3. Characterize Host Responses to Infection and Disease
4. Characterize Virulence Factors

Objective 1.1 Evaluate Factors Contributing to *Coccidioides* Geographic Spread

Although most cases of coccidioidomycosis in the United States are seen in Arizona and California, the disease is also found in many arid and semi-arid regions throughout both American continents and cases have been identified in most states in the United States due to travel to endemic areas. Increases in the number of coccidioidomycosis cases have been associated with increasingly hot and dry weather conditions, suggesting that climate and changes in weather may also affect the geographic range and incidence of *Coccidioides* infection. Locally acquired cases have been detected outside of the traditional endemic regions, including in Eastern Washington, Oregon, and Northern California. Further research is needed to understand the factors that contribute to *Coccidioides* prevalence and spread in the environment.

The uneven distribution of *Coccidioides* in soil, including in areas undergoing outbreaks indicates that factors such as temperature, moisture, and soil composition may affect fungal persistence and survival in the environment. Animal reservoirs have not been definitively determined. Small mammals, including rodents, may be reservoirs of *Coccidioides* that help facilitate spread to new geographic areas. NIAID is supporting research to correlate environmental changes and pathogen prevalence with the risk of *Coccidioides* infection. A more comprehensive evaluation of environmental factors and natural reservoirs contributing to

Coccidioides persistence and spread will better define areas of endemicity and identify populations at risk for Valley fever.

In addition to environmental factors, fungal-specific factors may also contribute to dissemination. These changes may be elucidated through more comprehensive genomic evaluations and comparisons of the two *Coccidioides* species. These studies may provide insights into the organism's survival strategies within different ecological niches and enhance our understanding of disease spread.

Objective 1.2 Improve Understanding of *Coccidioides* Biology and Life Cycle

Coccidioides are dimorphic fungi, exhibiting alternate morphological forms in the soil and animal host (Figure 2). In the soil, the fungus forms arthroconidia (or spores) that can become airborne. Once inhaled by a mammalian host, the arthroconidia transition to a parasitic phase, dividing and enlarging into spherules. The mature spherule eventually ruptures and releases numerous endospores. These endospores can spread to any organ system and in rare instances establish disseminated disease in the host that may require life-long antifungal therapy.

This unique dimorphism presents challenges for immune detection and activation. There is a functional understanding of very few genes in *Coccidioides* spp. Genetic studies to increase understanding of *Coccidioides* biology during infection will help identify virulence factors, phenotypic variation, essential metabolic pathways, and immunogenic antigens that may be exploited as targets for vaccine development. To sustain this discovery research, NIAID will continue to prioritize the advancement of genetic tools and molecular resources to delineate *Coccidioides* biology and life cycle.

Objective 1.3 Characterize Host Responses to Infection and Disease

While most healthy individuals infected with *Coccidioides* spp. experience an uncomplicated recovery and life-long immunity, individuals with suppressed or compromised immune systems are at higher risk for disseminated disease and severe clinical outcomes which indicate that the host immune response plays a critical role in disease progression. Given that individuals who have been infected are mostly resistant to re-infection, it is likely that immune responses to *Coccidioides* can confer lasting immunity from disease. The specific mechanisms of this long-term protection and the molecular and cellular immune events leading to severe disease are not well understood.

Previous studies on Valley fever suggest that both innate and adaptive immunity may be essential for the control of *Coccidioides*, but it remains unclear how these two arms of the immune system coordinate to clear the infection and establish durable immunity. Studies in animal models demonstrate that the innate immune response is important for recognition and

control of *Coccidioides* infection, with specific C-type lectin-like receptors and Toll-like receptors playing an essential role in the protection against infection and dissemination, respectively. While neutrophils and macrophages are known to be involved, the role of other innate immune cell types such as natural killer cells, dendritic cells, and eosinophils are poorly understood. Studies have also indicated that T-cells, particularly Th1 and Th17 responses contribute to adaptive immunity against Valley fever, but a better understanding of the cross-talk between the innate and adaptive immune responses required to produce lasting immunity to *Coccidioides* is needed.

Granuloma formation is a hallmark of Valley fever, yet the cellular ingredients required for the formation and maintenance of these complex structure is poorly characterized. It is unclear what cell types and signaling pathways are involved and little information is available about the immune microenvironment within the granuloma. Understanding the cellular communication pathways associated with granulomas during different disease states may yield clues to identify protective and permissive host responses to *Coccidioides*.

Additionally, individuals with certain genetic ancestries, such as Native Americans, Black and African Americans, Latinos, and Filipinos are at increased risk of developing disseminated disease, suggesting that genetic variants may impact host control of the pathogen and contribute to severe disease. However, the complex molecular pathways linking genetic ancestry and a dysregulated immune response leading to disease rather than dormant infection are poorly understood. Studies are needed to characterize genetic and other factors associated with protective or adverse clinical outcomes in populations at higher risk for disease. For example, large-scale, longitudinal cohorts would be useful for the detection of alleles associated with genetic risk. Machine learning may also aid in uncovering the genetic links to severe disease outcomes at the individual level.

To meet this objective, NIAID is prioritizing research that will provide a basic foundation for an understanding of the innate and adaptive immune response to *Coccidioides*. This effort will include characterizing the immunological compartments that coordinate and maintain immunity and describing human genetic and immunological risk factors that contribute to disease. The identification of host immune mechanisms and correlates associated with protection from disease after infection, or the progression to mild or severe disease will be crucial to guiding the development of a safe and effective vaccine for Valley fever.

Objective 1.4 Characterize Virulence Factors

Although many cases of Valley fever are asymptomatic and self-limiting, approximately 40 percent of infected individuals develop significant flu-like symptoms in the weeks following inhalational exposure. In some cases, individuals experience spread of disease throughout the

body including to the brain, skin, or bones. The factors that drive pathogenesis in one particular organ system within an individual host are unknown.

Identifying virulence factors that aid *Coccidioides* survival and immune evasion in the host has been hampered by the lack of genetic tools to manipulate gene expression and observe phenotypic changes. The unique dimorphic nature of *Coccidioides* also adds complexity to characterizing basic virulence factors. Currently, only a handful of virulence factors have been identified. The most thoroughly described are the spherule outer wall SOWgp and Mep1 that digests SOWgp to aid immune evasion during endospore formation. Additionally, a urease and a master transcription factor controlling expression of pathways essential for pathogenesis have been linked to virulence in the mammalian host. Given the dearth of identified *Coccidioides* virulence factors, further studies are needed to elucidate the fungus-specific mechanisms that contribute to modulating pathogenesis, evading host detection, promoting dissemination, and enhancing disease severity. NIAID will continue to support research on virulence mechanisms associated with *Coccidioides* infection to expand our knowledge on *Coccidioides* pathogenesis and to identify targets that can be exploited for vaccine development.

Strategic Priority 2: Develop Tools and Resources to Support *Coccidioides* Vaccine Research

Biomarkers, assays, and animal models are essential tools and resources for testing new vaccines and advancing Valley fever clinical studies. The identification of fungal and host biomarkers also support clinical trials by potentially serving as surrogate endpoints to help predict whether a vaccine is likely to have a desired effect in early-stage trials of candidate vaccines. Multi-disciplinary collaborations will also be needed to promote sharing of resources, tools, data, and samples for basic research, product testing, and clinical evaluation of promising vaccine candidates.

Strategic Priority 2: Develop Tools and Resources to Support *Coccidioides* Vaccine Research

1. Advance Development of Biomarkers and Rapid Point-of-care Diagnostics
2. Develop Cell Culture and Animal Models that Reflect Human Disease
3. Leverage and Expand Clinical Capacity to Promote Collaboration

Objective 2.1: Advance Development of Biomarkers and Rapid Point-of-care Diagnostics

Early symptoms of Valley fever are often difficult to distinguish from other pulmonary infections. Rapid and reliable point-of-care diagnostics that distinguish among uninfected individuals, people with active infection, and those with previously established immunity will be required for successful clinical development and testing of candidate vaccines. To prevent diagnosis delays, the assays should also be rapid and deployable in primary health care settings without a requirement for special equipment or personnel. NIAID will continue to support novel approaches to develop rapid point-of-care diagnostic tests for Valley fever. To address the need for new and improved diagnostics, significant efforts will be required to identify biomarkers that can be integrated into diagnostic platforms to provide accurate, reliable, and actionable information to clinicians. Reliable and convenient diagnostics also will improve patient care while vaccine development is underway.

New molecular diagnostics are needed for the direct detection of the pathogen. Conventional methods for diagnosing Valley fever rely primarily on culture methods, histopathology, and a variety of serologic assays that detect *Coccidioides*-specific IgG and IgM antibodies. While these serologic tests are clinically useful, they have limitations. By looking for antibodies as a marker of infection, serological tests do not detect the presence of a pathogen directly. Therefore they may miss an early infection when antibodies have not yet been produced. Conversely, in certain clinical contexts such as immunocompromised hosts, antibody titers may not reflect disease stage, severity, or clinical response to therapy.

As highlighted in Figure 2, *Coccidioides* has a complicated lifecycle within the human body and may cause a heterogeneous clinical spectrum. Primary disease mostly affects the lungs and is initiated by direct inhalation of arthroconidia. Secondary disease also affects the lungs and can become a chronic process. Disseminated disease (usually resulting from spread of a primary lung infection) can involve many organs including the skin, bones, joints, nervous system and meninges. The ability to detect the fungus accurately in this wide variety of tissues is challenging and may require different diagnostic approaches. In order to systematically test vaccine candidates the ability to accurately and uniformly diagnose individuals is paramount regardless of the stage of disease or the tissue affected.

In addition to serving as the basis for clinical diagnosis and prognosis, identifying fungal and host biomarkers will be essential to facilitate clinical trials and may serve as surrogate endpoints in early stage trials of candidate vaccines. Surrogate endpoints may predict whether a vaccine is likely to have the desired protective effect and advance to later stage clinical testing. It is preferable that biomarker signatures come from easily obtainable samples such as peripheral blood, urine, stool, or volatiles, such as compounds that may be measured in the

breath. NIAID will continue to support the identification and validation of host biomarkers to distinguish disease stages and response to interventions.

Objective 2.2: Develop Cell Culture and Animal Models that Reflect Human Disease

The diverse pathology of Valley fever in humans combined with the biosafety level 3 (BSL3) containment conditions required for laboratory experiments in *Coccidioides* presents challenges in the development of robust cell culture and animal models of disease that recapitulate human infection. Currently, mice are the primary animal model used in *Coccidioides* research and preclinical studies. However, *Coccidioides* infections have been shown to progress more rapidly in mice compared to humans, although advances have been made using genetically altered mouse strains and attenuated *Coccidioides* to recapitulate human disease. Rabbit models have been developed, but given BSL3 requirements, rabbits are more costly and more difficult to manage. Naturally infected dogs and nonhuman primates (NHPs) in facilities located in endemic regions present opportunities to follow the diverse disease states but these types of approaches may lack statistical rigor.

Additional animal models are needed that recapitulate both pulmonary and disseminated disease states in humans. Mice are a very well-established model for Valley fever, but present some limitations since *Coccidioides* infection progresses rapidly in mice and the pharmacokinetics of drugs may differ significantly from humans. Other small animal models could be developed that more closely mimic human disease. Additionally, there could be opportunities to study and treat naturally infected dogs or NHPs in primate centers within the endemic area. Developing cutting edge *in vitro* models including organoids and mixed primary cultures that recapitulate the lung epithelium will serve as valuable, cost-effective complements to animal models. NIAID will continue to support small and large animal models of *Coccidioides* and novel cell and tissue culture techniques to deepen the understanding of the host-pathogen interaction.

Objective 2.3: Leverage and Expand Clinical Capacity to Promote Collaboration

Advancing Valley fever research toward the development of a vaccine will require leveraging and expanding clinical research capacity to promote collaboration. Multidisciplinary collaborations foster resource-sharing across disciplines which may result in better approaches for identifying clinical research sites and recruiting relevant populations. It would also foster training and development of innovative Valley fever researchers. To support this objective, NIAID has established a network of [Coccidioidomycosis Collaborative Research](#)

Centers. These multi-disciplinary research teams conduct both clinical and basic research and will collaborate to investigate potential diagnostics, therapeutics, and vaccines for Valley fever.

NIAID also funds multiple networks that can design and implement clinical trials for testing candidate vaccines and has clinical trial units dedicated to supporting vaccine research (Appendix 4). NIAID will continue to build on its existing tools, resources, and investments in clinical research infrastructure and resources where Valley fever is endemic in the United States.

Strategic Priority 3: Develop and Advance Vaccines to Prevent Coccidioidomycosis

Developing a vaccine to prevent coccidioidomycosis will require building on insights gained into the biology of Coccidioides and the immune mechanisms preventing or limiting disease. Ideal vaccine candidates should adhere to specific criteria (appendix 1) including being safe and effective in all populations, particularly individuals who are immunocompromised and at highest risk for disease.

Strategic Priority 3: Develop and Advance Vaccines to Prevent Coccidioidomycosis

1. Support and Advance Rational Design of Vaccines for Valley fever
2. Test Vaccine Candidates in All Populations

Objective 3.1: Support and Advance Rational Design of Vaccines for Valley fever

No fungal vaccines are currently approved for human use in the United States by the Food and Drug Administration (FDA). Nonetheless, the development of a prophylactic vaccine against coccidioidomycosis should be feasible because patients who recover from infection can acquire long-term immunity. Because of this, there is a long history of research on coccidioidomycosis vaccines. Early promising efforts included immunizing mice and NHPs with formalin-killed spherules. However, clinical trials using this strategy were stopped after the killed spherule vaccine did not demonstrate significant reduction of incidence or severity of disease and because of observed safety signals. Since then, advanced live-attenuated vaccine strategies have been evaluated that demonstrated efficacy in mice and dogs. Live-attenuated vaccine platforms will require rigorous testing to ensure safety, especially in immunocompromised individuals who typically are at risk for severe Valley fever.

Recombinant subunit protein-based vaccine candidates offer an alternative to live-attenuated vaccine candidates. Many surface antigens of the spherule have been evaluated as potential

vaccine targets. In previous studies in animal models, vaccines using a single antigen provided modest to moderate protection, suggesting multivalent vaccines may be needed for this approach. In this regard, an NIAID-supported recombinant protein approach used a multivalent polypeptide antigen comprised of three *Coccidioides* protein fragments and five human T-cell epitopes, and Glucan Chitin Particle (GCP) adjuvant. This vaccine candidate was shown to elicit a protective Th1/Th17 mediated immune response in mice, and the adjuvant requires further development before first in human studies can be initiated.

To develop a safe and effective vaccine for the diverse populations at risk for Valley fever, including individuals who are immunocompromised, multiple vaccine approaches guided by rational vaccine design will be needed. Research into adjuvants will be crucial to enhance vaccine effectiveness. In particular, adjuvants that promote and sustain durable Th1/TH17 immunity will be important. To support this effort, the [NIAID Adjuvant Discovery Program](#), the [NIAID Adjuvant Development Program](#), and [NIAID Preclinical Services](#) could be leveraged to advance novel adjuvants, improve the breadth and durability of novel immunogens, and evaluate vaccine delivery platforms.

Objective 3.2: Test Vaccine Candidates in All Populations

An ideal Valley fever vaccine for humans would need to be safe and effective in all populations, especially immunocompromised people, who are at highest risk of disease. Although previous studies in mice and dogs have highlighted the promise of a live-attenuated vaccine against *Coccidioides*, additional vaccine strategies will be necessary to achieve protection in more vulnerable populations for whom a live-attenuated vaccine may not be appropriate. Certain additional co-infections will need to be considered depending on geographic origin. For example, co-infections with tuberculosis and other regional mycoses, such as histoplasmosis, are prevalent in Latin and South America, and could affect responses to a Valley fever vaccine.

Vaccine trial participants will need to reflect the populations most at risk of infection and the particular susceptibilities to disease. Additionally, prior studies have shown that a significant number of people in endemic regions possess some amount of immunity to *Coccidioides* from prior infections. The immune status of these individuals will need to be considered when conducting eligibility screening for enrollment into a Valley fever vaccine trial.

Conclusion

The NIAID *Strategic Plan for Research to Develop a Valley Fever Vaccine* establishes scientific research priorities that will inform the development of a vaccine to address this growing public health need. This effort will require a continued commitment to advancing basic research on the biology of the pathogen and the immune response to it, the development and sharing of tools and resources to support the scientific community, and the development and testing of

promising vaccine candidates. These scientific priorities build on the framework of previous successful vaccine development efforts. To support these efforts, NIAID will also continue to work with public health stakeholders and support collaborations to promote Valley fever research.

Appendix 1. Valley Fever Strategic Plan Working Group Members

Last Name	First Name	Position
Azeez	Olumayowa	Health Science Policy Analyst, Policy, Planning and Evaluation Branch, OD, NIAID
Bushar	Nicholas	Chief, Policy, Planning and Reporting Section, Policy, Planning and Evaluation Branch, OD, NIAID
Dixon	Dennis	Chief Bacteriology and Mycology Branch, Division of Microbiology and Infectious Diseases, NIAID
Ford	Andrew	Program Analyst, Office of Scientific Coordination and Program Operations, Division of Microbiology and Infectious Diseases, NIAID
Love	Dona	Mycology Program Officer, Division of Microbiology and Infectious Diseases, NIAID
Miers	Sarah	Program Analyst, Office of Scientific Coordination and Program Operations, Division of Microbiology and Infectious Diseases, NIAID
Perdue	Sam	Microbiologist, Division of Microbiology and Infectious Diseases, NIAID
Robinson	Daphne	Health Science Policy Analyst, Policy, Planning and Evaluation Branch, OD, NIAID
Schneider	Johanna	Director, Office of Strategic Planning, Initiative Development & Analysis, OD, NIAID

Appendix 2. Analysis of Public Comments to Request for Information (RFI)

NIAID sought input from stakeholders in the scientific research community and the general public regarding the proposed priorities through a Request for Information (RFI). The RFI ([NOT-AI-22-026](#)) was open for comments from February 2, 2022, to April 5, 2022. Comments were submitted through a web-based form or by email. Comments were requested on, but were not limited to, the following topics in *Coccidioides* research:

- Significant research gaps and/or barriers not identified in the strategic priorities above
- Identification of items most likely to facilitate vaccine development
- Necessary resources critical to advancing research in the three strategic areas
- Emerging scientific advances or techniques that may accelerate research related to the three priorities
- Approaches to increase marketability of a vaccine and facilitate collaborations with industry

NIAID received 13 responses to the RFI, mostly from academia and private companies. Overall, the submissions supported both the effort to develop a plan and the specific priorities. No new priorities were suggested. The comments below provided further details on what to include within each priority.

Input regarding Priority 1—Basic Research

- Clinical manifestations across racial and ethnic groups
- Clinical differences across the lifespan
- Immune mechanisms underlying various clinical manifestations
- Genetic susceptibility to infection
- Real incidence, including subclinical cases
- Spherulation-specific genes, and mechanism of spherulation
- Immune responses to endospheres, and to early and late spherules
- Detailed genetic sequencing and annotations, bioinformatics expertise
- Phenotypic variations among strains
- Identify immune responses that are protective and those that contribute to disease
- Role of mucosal immune responses
- Pathogenesis in special patient populations, including pregnant women

Input regarding Priority 2—Tools and Resources

- Simple screening methods: PCR on urine, simple EIA immunodiffusion, skin test for chronic carriers

- Biobanks with blood samples, chest X rays, isolates, tissue samples, with relevant clinical information
- Reagents such as cocci antigens and antibodies, recombinant proteins, peptides, novel immunogens
- Access to commercial diagnostic tests for research
- Better animal models (especially NHPs) and humanized animal models

Input regarding Priority 3—Vaccines and Therapeutics Development

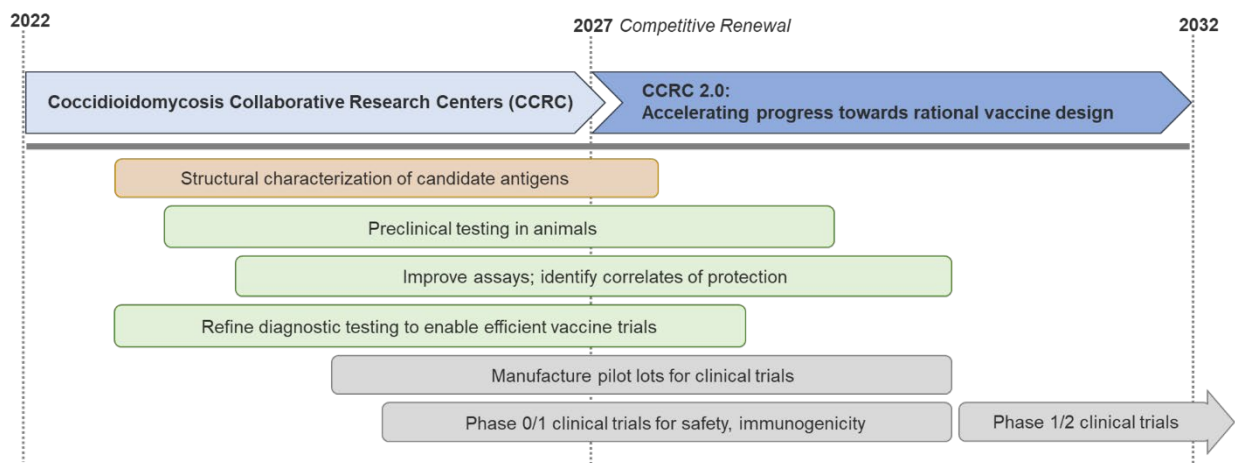
- Identify correlates of protection for clinical testing (regardless of mechanism)
- Develop cocci-specific fungicides, especially one that enters CNS for meningitis
- Develop post-exposure therapeutics
- Target vaccine against spherules and endospores
- Develop nucleic acid vaccines
- Test new adjuvants, make adjuvants available for preclinical testing
- Define vaccine success: prevent symptomatic pneumonia and disseminated disease
- Broad protection against several fungi would help commercialization
- Support to test canine vaccine in humans
- Clinical trial recruitment via military, Dept of Veterans Affairs (VA), ER or urgent care

The RFI responses reflected the numerous challenges in the development of a Valley fever vaccine. The working group members carefully considered all the suggestions and incorporated them in the plan as appropriate.

Appendix 3. Vaccine Development Benchmarks, Criteria, and Market Analysis for a Valley Fever Vaccine

Benchmarks

The *Strategic Plan for Research to Develop a Valley Fever Vaccine* reflects the fundamental research priorities that are necessary to develop a Valley fever vaccine. Supporting research aligned with these scientific principles, along with critical research infrastructure, including the Coccidioidomycosis Collaborative Research Centers, NIAID will continue to advance the vaccine development process over the next decade.



Appendix Figure 1: Benchmarks in the Valley fever vaccine development process.

Vaccine Criteria

To most effectively protect public health, optimal Valley fever vaccines should align with specific criteria outlined below.

A Valley fever vaccine should:

- Utilize vaccine platforms (and adjuvants) that are suitable for use in immunocompromised populations such as recombinant proteins and nucleic acid delivery platforms
- Be at least 75 percent effective at preventing symptomatic *Coccidioides* spp. disease and preferably infection
- Have durable protection that lasts at least 1 year and preferably lifelong protection
- Be suitable for all age groups and special populations, including immunocompromised and at risk populations

Target Product Profile (TPP) Characteristics

	Minimal	Optimal
Goal	Prevent disease	Prevent infection
Age range	All adults	All ages
Special populations	Safe and effective in immunocompromised	Safe and effective in all populations
Species covered	<i>C. immitis</i> and <i>C. posadasii</i>	<i>C. immitis</i> and <i>C. posadasii</i>
Durability of protection	Lifelong with yearly boosters	Lifelong after priming regimen
Vaccine platforms	Suitable for use in immunocompromised people (i.e., recombinant protein, mRNA)	Suitable for use in immunocompromised people (i.e., recombinant protein, mRNA)

Market Analysis

In 2020, the FDA determined that a significant market may exist for coccidioidomycosis preventatives, including a vaccine, in developed nations such as the United States. ([Federal Register: Notice of Decision Not To Designate Coccidioidomycosis as an Addition to the Current List of Tropical Diseases in the Federal Food, Drug, and Cosmetic Act](#)). Although changing epidemiology and preferred product profile characteristics may alter these conclusions once candidate antigens and candidate products are identified, these findings reaffirm the public need for continued advancement of Valley fever research, including the development of a safe and effective vaccine. This Notice also underscores the need to continue to engage with industry partners as candidate vaccines are identified and progress through preclinical testing. In future workshops on Valley fever vaccine development, NIAID will include analyses of factors that could impact the Valley fever vaccine market, along with market-shaping tools, such as projected cost-effectiveness of a candidate vaccine.

Appendix 4: NIAID-Supported Valley Fever Research Resources

Resource Name	Description
<u>BEI Resources Repository</u>	Central repository that supplies organisms and reagents to the broad community of microbiology and infectious diseases researchers
<u>Bioinformatics Resource Centers</u>	Collects, archives, updates, and integrates research data with user-friendly interfaces and computational analysis tools
<u>Coccidioidomycosis Collaborative Research Centers</u>	Highly collaborative, multidisciplinary research teams to conduct translational and clinical studies for the improved diagnosis, treatment, and prevention of coccidioidomycosis
<u>NIAID Clinical Genomics Program</u>	Provides centralized resources to be used for genomics and related research
<u>Genomic Centers for Infectious Disease Resources</u>	Provides innovative application of genomic technologies and rapid, cost-efficient production of high-quality genome sequences for pathogens, and hosts
<u>ImmPort</u>	Platform to share and analyze immunology data generated from human and animal models
<u>Immune Epitope Database and Analysis Resource</u>	Database with detailed information for more than 1,000,000 unique immune epitopes (antibody/B cell and T cell) related to infectious and immune-mediated diseases
<u>ImmuneSpace</u>	Powerful data management and analysis engine for the HIPC program that enables integrative analyses and visualization of human immunological data
<u>Interventional Agent Development</u>	Services to facilitate preclinical development of therapeutics and new <i>in vivo</i> diagnostics for infectious disease-causing pathogens and/or toxins
<u>NIAID Adjuvant Development Program</u>	The goal of the adjuvant development programs is to establish and expand the availability of novel vaccine adjuvants that researchers can use for preclinical vaccine development in both infectious and immune-mediated diseases
<u>NIAID Adjuvant Discovery Program</u>	NIAID plays a leading role in the discovery, development, and characterization of new vaccine adjuvants that may be used to: improve the efficacy of current vaccines; design new or improved vaccines for existing and emerging infectious diseases; and develop

Resource Name	Description
	vaccines to treat allergies, autoimmune diseases, and cancer
<u>NIH Tetramer Core Facility</u>	Produces and distributes major histocompatibility complex tetramers and related reagents to the research community
<u>Phase I Clinical Trial Units for Therapeutics</u>	Support design, development, implementation, and conduct of Phase I clinical trials against viral (other than HIV), bacterial, parasitic, and fungal pathogens
<u>Preclinical Models of Infectious Disease Program</u>	Provides development, screening, and efficacy testing in preclinical infectious diseases models, including traditional lab species, nonhuman primates, and non-traditional models
<u>Structural Genomics Centers for Infectious Diseases</u>	Applies state-of-the-art technologies/methodologies to characterize 3-D atomic structures of molecules to support infectious disease research
<u>Therapeutic Development Services: Biopharmaceutical Product Development Services</u>	Offers services for biotechnology products, such as planning, product characterization, process development, formulation, Good Manufacturing Practice, and Chemistry, Manufacturing and Control documentation
<u>Therapeutic Development Services: Interventional Agent Development Services</u>	Facilitates development of therapeutics, including lead identification and development, chemistry and manufacturing, toxicology, and pharmacokinetics
<u>Vaccine Adjuvant Compendium</u>	Displays adjuvant characteristics or metadata defined through NIAID-supported adjuvant studies, helps vaccine developers identify suitable adjuvants for vaccine indications
<u>Vaccine Development Services: Vaccine Testing Services</u>	Offers services for vaccine and adjuvant development such as assay development, non-clinical immunogenicity and efficacy studies, clinical and non-clinical sample testing and safety and toxicity testing
<u>Vaccine Development Services: Vaccine Manufacturing Services</u>	Feasibility, Gap Analysis, and Product, Development Plan Support, Product Optimization, Process Development and Formulation Studies, Product Release Assay Development including Potency Assays, Pilot and cGMP Manufacture, Audits and Regulatory Activities and Documentation, Preclinical Services for vaccines
<u>Vaccine and Treatment Evaluation Units</u>	Support efforts to develop new and improved vaccines and therapies against infectious diseases