October, 2022.

Welcome to the Valley Fever Center for Excellence's website. Here we try to provide reliable and timely information about coccidioidomycosis, the medical name for Valley fever.

November 12th through 20th is Valley Fever Awareness Week, the 20th year that the Valley Fever Center for Excellence has hosted it. Elsewhere on our website is a description of the several activities that are planned during the week, but I would like to highlight one in particular, a Valley fever workshop to be conducted by the National Academies of Science, Engineering, and Medicine on November 17th and 18th. The first day will focus on the various economic and public health problems that Valley fever poses for humans, dogs, and many other species, and the second will turn to the opportunities that exist to reduce Valley fever's impact, some within immediate reach. The workshop is open to the public, it will be held both in person and on the web, and there is no cost to register by going to https://www.nationalacademies.org/event/11-17-2022/impact-and-control-of-valley-fever-a-workshop. Afterwards the Academies will make the sessions available in their archives.

The idea for the Academies workshop emerged from the very exciting progress that has been made at the Center towards developing a vaccine that has the very real potential of preventing Valley fever in people. The idea of a workshop was first raised in early 2020 as a possible way to heighten awareness about this very important disease, but it was quickly side-lined by the rapid emergence of the SARS-CoV-2 pandemic. As the pandemic become more manageable, the workshop idea resurfaced, the funding was found to underwrite it, and an organizing committee created the program. Although the scope of the workshop extends broadly across all aspects of what Valley fever is, the last sessions focus on approaches to vaccine development.

Since nearly all persons who become infected with the Valley fever fungus (*Coccidioides* species) develop immunity to second infections, the idea that a vaccine might do that as well has been a dream for nearly three-quarters of a century. In fact, a vaccine that showed protection in mice actually was tested in people in the 1980s. While that vaccine fell short, the success of conducting the trial showed that it was possible to test a future vaccine in humans once a more promising vaccine candidate was discovered. Since then, the field of vaccine technology has expanded by taking advantage of the new biology of genetics. At the University of Arizona, Marc Orbach made a critical discovery that genetically removing a specific gene from the fungus resulted in a mutant which no longer was able to cause disease in mice, even those that were immunologically defenseless. With further work, it now appears that the decreased invasiveness of the mutant is because it is unable to complete a first generation of growth in mammalian tissue. Lisa Shubitz then discovered that if spores of this mutant were used to vaccinate mice, those vaccinated animals were very resistant to getting ill from a subsequent infection with the normal dangerous Valley

fever fungus. Over the next several years many experiments with mice confirmed and expanded upon these original observations. This body of work, paid for by philanthropic donations to the Valley Fever Center, was the basis for the Valley Fever Center in collaboration with Anivive Biopharma, a commercial partner, to win in 2016 a research grant from the NIH to use the gene-deletion mutant as a vaccine to prevent disease in dogs. Last year, Dr. Shubitz and her co-workers published their studies that demonstrated protection in experimentally infected dogs, a requirement of the United States Department of Agriculture for any vaccine to obtain a veterinary licensure. The NIH grant was awarded on the argument that if the vaccine could show protection in dogs, that would provide major encouragement that it might also be used in humans. Now that dogs have been shown to be protected, it now seems the right time to continue the work toward humans.

Overall costs for going from where we are now with the gene-deletion vaccine all the way to FDA approval is expensive, perhaps $200 to $300 hundred million dollars. That would not be an unreasonable expense, considering that the economic impact of Valley Fever is approximately $1.5 billion annually. However, support from federal or state agencies is almost certainly needed to initiate this program, and the essential first steps toward human trials are much less expensive than the eventual large clinical trials of vaccine efficacy. For example, creating the recipe for the exact formulation could be done for two or three million dollars. Similar amounts could fund pre-clinical toxicology studies to assure safety. Such amounts might be much more easily found, especially if the many stakeholders, such as fire-fighters, construction workers, prison systems, and retirement communities, made their interests in a preventative vaccine known.

Even thinking about conducting human vaccine studies was only a concept a decade ago. Now, with the Valley fever vaccine invented at the University of Arizona, we are on to the problem of making the studies happen. Challenging but great progress, and the direct result of there being a Valley Fever Center for Excellence.