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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.

The Food and Drug Administration (FDA) coined the phrase, "Orphan Disease," for relatively uncommon medical conditions (https://www.fda.gov/media/99546/download). They include not only truly rare diseases, cataloged by the NIH at https://rarediseases.info.nih.gov/, but also other diseases with less than 200,000 United States' patients with the condition. While 200,000 may seem like a large number, spread across the entire country, it means less than one in a thousand citizens are concurrently affected. The reason for identifying these diseases as "orphan" was to highlight the lack of commercial incentive that typically exists to develop new therapies or vaccines for a disease that is infrequent and so represents a very small market needing the product. In 2005, the University of Arizona, when it became the sponsor of nikkomycin Z development [1], received acknowledgement from the FDA Office of Orphan Drug Development that Valley fever was, indeed, an orphan disease.

The paradox of this designation is that within the endemic regions of the Western United States [2], Valley fever is anything but rare. For example, pneumonia in the general population is very common. Within the population centers of Arizona, one quarter to one third of these infections are Valley fever [3, 4]. Reported infections within California and Arizona in some years have exceeded 20,000 infections [5], and the number of unrecognized infections is thought to be several fold greater [6]. For residents within regions endemic for Valley fever, its morbidity is comparable to that of polio, measles and chicken pox before these world-wide viral infections were controlled [7, 8]. Recent studies of the economic impact of Valley fever on California and Arizona find it to be over $1.4 billion annually [9, 10]. Because of its importance to those living where Valley fever is common, it is especially important that they know about it and understand how it could be better addressed if attention was brought to bear on this unmet need.

From genetic analyses, the fungus, *Coccidioides*, appears to have been present on the earth for over five million years when its two currently recognized species, *C. immitis* and *C. posadasii* diverged [11]. Interestingly, at a Nebraska archeology site, an 8,500-year-old bison was found to have had coccidioidomycosis [12], giving strength to the idea that the endemic regions for Valley fever might change over time with evolving weather patterns. Even so, the first human Valley fever infections were only identified at the end of the 19th century [13, 14] and it was not until the 1930's that the serious, often life-threatening, infections seen at Stanford Hospital and other academic centers were the most extreme manifestations of the common and typically self-limited illness known to residents of Bakersfield and Kern County, California as San Joaquin Valley fever [15]. Despite this discovery, through the first half of the twentieth century,

endemic regions for Valley fever were rural, not heavily populated, and so total numbers of persons infected were relatively small. How population shifts would bear on the impact of Valley fever was first evident when large-scale military training of new recruits to fight in World War II was conducted in California's Central Valley [16-18]. Since then, metropolitan Phoenix has become a major population center of approximately 4.5 million people and Counties surrounding Phoenix are also experiencing rapid population expansion. The same sort of growth is also occurring in California to increasingly involve the Southern Central Valley.

Since the 1930's, residents of Bakersfield and the surrounding Kern County have been on the forefront of bringing attention to Valley fever and to the need for better ways to manage it. This has had substantial impact on both scientific advances and governmental responses to address this disease. The medical and scientific contributions by the Bakersfield community vary widely:

- When the very first effective antifungal drug, amphotericin B, became available, Bakersfield and other Central Valley physicians pioneered its effective use to treat coccidioidal meningitis [19, 20]. In subsequent years, physicians at Kern County Medical Center were active collaborators with the NIH-sponsored Mycoses Study Group [21, 22].
- Bakersfield was one of the three study sites for a human study of an early Valley fever vaccine. Although, that vaccine candidate was found not useful, it showed how such trials could be conduct in the future [23]. Two decades ago, California State University Bakersfield administered the Valley Fever Vaccine project, a five-laboratory collaboration to discover a more effective preventative vaccine [7]. That program laid the ground work for an advanced recombinant vaccine [24] and an avirulent gene-deletion vaccine which is currently in development by UArizona as a canine veterinary product and potentially for human clinical trials [25, 26].

Kern County residents have also been politically mobilized to find legislators that understand the importance of Valley fever to their community. The Valley Fever Vaccine Project was supported in large part by California State funds, and, more recently, several million California tax dollars have been directed to address Valley fever in general, and the Kern Valley Fever Institute in particular. When first elected as the district 23 representative to the U.S. Congress, Kevin McCarthy established the Congressional Valley Fever Task Force, co-chaired by David Schweikert of Arizona. As evident from Congressman McCarthy's website (https://kevinmccarthy.house.gov/issues/valley-fever), he is very proud of his accomplishments to promote more resources to better control Valley fever.

Since Arizona has more Valley fever infections than California, there is every reason for it to be as active as is California. The primary motivation for the founding of the Valley Fever Center for Excellence twenty-five years ago was to create an institutional commitment by the University of Arizona, the state's land-grant university, to addressing the state's very important public health problem. Since then, the Center has expanded

the number of scientists and clinicians working on Valley fever and have contributed over 80 scientific publications to aspects of Valley fever including fungal genetics, climate effects, immunity (including the vaccine work mentioned above), diagnosis, and therapeutics. In partnership with Banner Health, the Valley Fever Center for Excellence is seeking to improve the rate of early diagnosis of Valley fever by providing resources to frontline clinicians in primary, urgent, and emergency care units, enabling them to appropriately test patients for Valley fever and to manage new infections correctly when they are diagnosed. These materials are also available to the entire medical community on our website. Going forward and with additional funding, the Valley Fever Center could accelerate our progress by providing stipends for post-doctoral fellowships for young scientists and clinicians. The Center could also partner with departments throughout the UArizona campus to recruit new faculty who could then invest part of their career in better understanding and managing Valley fever. Also, I believe that the Congressional Valley Fever Task Force is an important forum for this disease to be discussed and for useful approaches to its management to be developed. It would make a great deal of sense for most, if not all, members of the Arizona congressional delegation to become members.

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