



FEATURED ARTICLE

Heightened Need for Awareness of Coccidioidomycosis

Coccidioidomycosis, also known as Valley Fever, has been drawing the attention of government officials and legislature. Last year, the California budget allocated \$8 million for research and outreach to combat the disease, with funding split between the University of California, the Valley Fever Institute at Kern Medical in Bakersfield, and the California Department of Public Health.

Part of the reason for increased attention is increasing incidence: California had a 213% increase (6/100,000 to 18.8/100,000) from 2014 to 2017 [1], and incidence is believed to be impacted by changes in temperature and precipitation [2-4]. California identified that heavy rainfall in March of 1991 and Feb-March of 1992, followed by drought, yielded an increased incidence of coccidioidomycosis in late 1991 and an even larger increase in 1992 [5]. Similar weather patterns were identified with rainy winters of 2016-17 followed by drought, and similar trends of increased incidence have been noted [1, 6]. The 328% increase in incidence from 1997-2013 in Arizona has been attributed to an increasing population, many of whom moved there from non-endemic areas and were not immune to *Coccidioides*, disruption of soil from new development, increases in reporting, and increased public and clinician awareness [6, 7]. Despite recommendations from public health departments, a low percentage of patients (2-13% in 2008) presenting with signs of community acquired pneumonia are being tested for coccidioidomycosis [8].

Coccidioidomycosis has not only increased in incidence, but also is appearing in areas not known to be endemic, though mostly attributed to travel to endemic areas (83%) [9]. A study in 2016 conducted surveillance in 14 states not known to be endemic (Louisiana, Michigan, Minnesota, Missouri, Montana, Nevada, New Mexico, North Dakota, Ohio, Oregon, Pennsylvania, Utah, Wisconsin, Wyoming) and found that of 186 patients surveyed, median time to diagnosis was 38 days, 70% were diagnosed with another disease before being tested for coccidioidomycosis, and 83% were prescribed antibiotics. Of those diagnosed with coccidioidomycosis from non-endemic states, 68% travelled to endemic states and 48% reside part-time in Arizona. This study recommended greater awareness nationwide among clinicians and the public to improve time to diagnosis and appropriate treatment [9]. A 2015 article by Benedict et al also identified coccidioidomycosis in areas not known to be endemic in patients or animals with no history of travel [10]. Chico, CA, Red Bluff, CA, Dinosaur National Monument in UT, and south-central Washington have been reported in the literature as having confirmed cases of coccidioidomycosis in geographic areas outside zones of endemicity [11-14]. Cano et al postulated that rodents may be reservoirs for *Coccidioides* and be capable of introducing microfoci in geographic regions not known to be endemic, potentially explaining an additional source of geographic spread [15]. Because many of the maps of endemicity were identified by large scale skin test surveys [16], and the reagents for these tests have not been available since 2000, estimates of incidence are believed to be 6 to 14 times higher than reported to public health [17]. Recently the FDA approved the skin test antigen, Spherusol, to detect delayed-type hypersensitivity but we are unaware of any current studies to re-assess epidemiology of coccidioidomycosis.

Additionally, concerning is the impact coccidioidomycosis has on patient quality of life. In the 2007 -2008 Arizona survey of 493 patients, they reported being symptomatic for 4 months, were unable to perform daily living functions for 47 days, three quarters of those employed missed a median of 2 weeks of work, and median time to diagnosis was 23 days [18].

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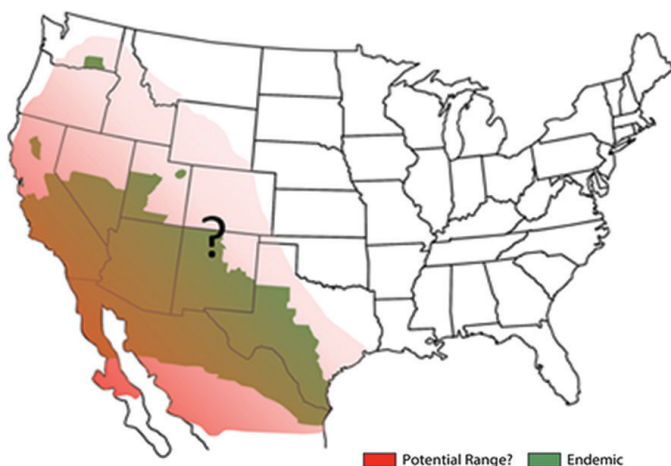
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The effects on healthcare and costs associated with diagnosis and treatment of coccidioidomycosis are considerable. From the 2007-2008 Arizona study, half the patients visited the emergency room and a quarter saw a healthcare provider more than 10 times [18]. Of patients with a primary or secondary diagnosis of coccidioidomycosis in 2007, the total hospital charges were \$86 million and the mean cost per hospitalization was \$49,000 [18]. A 2019 publication reporting cost burden in California calculated the total lifetime burden of 2017 coccidioidomycosis cases to be just under \$700 million when accounting for direct and indirect costs, and the lifetime per person costs were \$94,000 [1]. The costs per person ranged from \$23,000 for uncomplicated coccidioidomycosis pneumonia to \$1,023,730 for disseminated disease [1]. Of those with pulmonary nodules, 90% received diagnostic lung cancer work-up and had an average cost \$76,000.

Gorris et al described the possible effects of climate change on coccidioidomycosis endemic regions in the United States and estimated that currently 12 states are possibly endemic and up to 18 may be endemic by 2095 under moderate warming conditions, and the number of cases may increase by over 50% with the upper potential of mean cases to be 34,460 compared to 2018 CDC data of 9500 cases [19, 20]. They established a model based on the relationship between climate and Valley Fever incidence and created a climate-constrained model with climate projections from Earth system models to analyze future projections [20, 21]. They estimate that warmer climate conditions may expand coccidioidomycosis northward and drier counties with mountain rain shadows may be endemic; whereas, coastal areas with ample rainfall will not be endemic [19]. These climate predictions, along with evidence of increasing incidence, detection of coccidioidomycosis in areas where it was not previously seen, mobility of the population and relocation of immune-naïve individuals to endemic areas highlight the need for clinician and public awareness to expand beyond currently mapped boundaries.

Geographic Range of Valley Fever Potential



In summary, changes in the endemic pattern and incidence of coccidioidomycosis have occurred since the initial skin test surveys. Future changes are anticipated based on development of residential communities in the arid regions that were previously sparsely inhabited, land disturbances caused by excavation, and expansion north and east caused the impact of climate change on environmental conditions favoring growth of *Coccidioides* in the soil. Better methods for assessing immunity to *Coccidioides* are needed to define the current endemic pattern and determine the impact of factors that may change the endemic pattern in the future. Research to develop a cytokine release assay (CRA) like the interferon-gamma release assays (IGRA) used for determination of immunity to *Mycobacterium tuberculosis* may provide a similar method for determination of immunity to *Coccidioides* [22].

CDC Website. <http://www.cdc.gov/fungal/pdf/valley-fever-expanding-cocci-508c.pdf>; Edwards PQ, Palmer CE. *Dis Chest*. 1957;31:35-60.



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