# Coccidioidomycosis in Animals

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**Abstract**

A broad diversity of animals is susceptible to infection by *Coccidioides* species. However severe or disseminated disease in animals other than pet dogs is not commonly reported in the literature. It is unclear if these cases are indeed rare or if they are not diagnosed and reported. The awareness of coccidioidomycosis is increasing in the Central Valley of California and southern Arizona, but outside of these areas the disease is not often diagnosed. Cases outside the endemic region frequently have delayed diagnosis, and as summarized here for many animals, the diagnosis was not made until after euthanasia. Frequently, a fungal infection is not considered as a primary cause of death or disease, in spite of the fact that hundreds of thousands of these infections occur every year. In the USA, coccidioidomycosis cases reported rival the number of cases of tuberculosis and Lyme disease. Considering that it is likely that only 10% of infections nationwide are reported, this disease has significant burden in the USA. Disease burden in the rest of the Americas remains unknown. Clearly, better diagnostics, effective treatments, and development of vaccines would greatly improve public health and reduce economic costs associated with coccidioidomycosis. Additionally, a great deal of work remains to fully understand the ecology and basic biology of the causative agent.

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## 4.1 Phylogenetics and Population Structure

There are two distinct cryptic species within the genus *Coccidioides* (*Ascomycota*, *Pezizomycotina*, *Eurotiomycetes*, *Onygenales*, *Onygenaceae*): *Coccidioides immitis* and *C. posadasii* (Fisher et al. 2002). Previous phylogenetic analyses and morphological characterization showed that *Uncinocarpus reesii*, a keratinophilic saprotroph, is one of the closest related fungi to *Coccidioides* (Sigler et al. 1998; Pan et al. 1994). However, recent work reveals that *Amauroascus mutatus*, *A. niger*, *Byssoonygena ceratinophila*, and *Chrysosporium queenslandicum* are phylogenetically closer to *Coccidioides* than *U. reesii* (Whiston and Taylor 2015). Within the *Onygenaceae*, no other dimorphic human pathogens have been identified; however other animal pathogens exist (Sigler et al. 1998; Herr et al. 2001; Sigler et al. 2013). The *Ajellomycetaceae*, which are distinct from the *Onygenaceae*, include *Blastomyces dermatitidis*, *Histoplasma capsulatum*, *Paracoccidioides brasiliensis* (Untereiner et al. 2004), and *Emergomyces* species (Dukik et al. 2017).

The *Onygenales* contain at least these two families as well as the *Gymnoascaceae* and *Arthrodermataceae*, but these are still preliminary assignments, and more work remains to be done to understand the complete picture of phylogenetic relationships. The *Onygenales* are a sister order to the *Eurotiales*, and the class containing these orders, the *Eurotiomycetes*, includes a number of species that cause disease in both animals and plants (Wang et al. 2009). Several genomes of *Eurotiomycetes* have been sequenced, which allows for comparative genomic studies.

The current understanding of genetic population structure within *C. immitis* suggests the existence of two populations: San Joaquin/Central Valley California (SJV) and Southern California/Mexico (SDMX) (Fisher et al. 2001, 2002). The genetic population structure of *C. posadasii* suggests three main populations: Texas/South America (TXSA), Mexico, and Arizona. Limited gene flow occurs among populations. More effort to understand genetic diversity in Mexico and Central and South America is needed. Recent evidence for even smaller-scale population structure within Arizona was reported (Teixeira and Barker 2016). Yuma and Phoenix isolates are distinct from Tucson patient and soil isolates, which suggests there may be specific ecological adaptations between these two areas. The Sonoran Desert is a highly variable landscape, which ranges from desert upland/grassland (Tucson) to the lower elevation desert biome (Phoenix/Yuma). *Coccidioides* growing in the soil in these areas would experience different abiotic and/or biotic stressors (Fisher et al. 2007; Lacy and Swatek 1974).

Additionally, genetic diversity in environmental and veterinary isolates differs from the genetic diversity among isolates infecting humans (Teixeira and Barker 2016). Human clinical isolates therefore provide valuable insights into population structure; however, isolates obtained directly from the environment are necessary to truly understand fine-scale population structure and determine if certain regions (i.e., Tucson vs. Phoenix) support the growth and survival of specific genotypes. Perhaps more intriguing is that the pool of diversity in the environment is higher than what is observed to cause disease to the human population, even with a small number of isolates available for genetic comparisons. Environmental isolates of *Coccidioides*

exist, but they are difficult to obtain (Barker et al. 2012; Johnson et al. 2014; Litvintseva et al. 2015; Lauer et al. 2012; Brillhante et al. 2012; Baptista-Rosas et al. 2007; Fisher et al. 2007). Greater effort is needed to assess the environmental reservoir of *Coccidioides* in the environment and true population structure.

The first reported case of the disease was described by Alejandro Posadas over 120 years ago in Argentina (Posadas 1892). Granulomas in skin lesions resembling a protist were observed. In 1896, the organism was named *Coccidioides immitis*: "*Coccidioides*" for the suspected coccidium protozoan and "*immitis*" which is Latin for "not mild" (Rixford and Gilchrist 1896). In 1900, it was clearly shown by researchers working in California that the causative organism was a fungus. Ophuls (1905) named the protozoan-like structure a spherule, a parasitic stage of the life cycle of the fungus. The disease was considered rare and fatal, as these were the first category of cases to be recognized (Morris 1924; Ryfkogel 1908). However, this view was changed by five cases of acute infections from which patients fully recovered and proved that *Coccidioides* exposure could result in nonlethal illness (Dickson 1937).

## 4.2 Life Cycle of *Coccidioides*

*Coccidioides immitis* and *C. posadasii* are dimorphic fungi that switch between a mycelial phase and a spherule phase (Fig. 4.1). A switch from polar to isotropic growth occurs when a susceptible host inhales clonal arthroconidia, and the development of the unique infectious structure is initiated. The spherule matures and releases endospores, which may develop into new spherules or arrest growth. Mild or asymptomatic infections generally stay localized to the lungs. More severe infections can disseminate to other body sites (spleen, synovial joints, liver, kidneys, etc.), and endospores can cross the blood-brain barrier (Nguyen et al. 2013). The fungus can initiate mycelial growth from excised tissue or other biosamples (biopsy, sputum, synovial fluid, etc.) even at 37 °C, although how and when this occurs in nature are not known. High temperature, elevated $CO_2$ concentration/low oxygen, and specific nutrients all play a role in the formation, growth, and maintenance of the spherule/endospore cycle (Converse and Besemer 1959). Conditions consistent with development of spherules include shaking cultures at 37 °C, under 6–20% $CO_2$, with a liquid medium containing glucose, ammonium acetate, potassium phosphate, magnesium sulfate, and zinc sulfate at a pH of 6.3 (Breslau and Kubota 1964; Brooks and Northey 1963; Northey and Brooks 1962; Converse 1955). There is variation among strains, but generally mature spherules develop in 3–6 days (Pappagianis et al. 1956; Huppert et al. 1982).

Whereas *U. reesii* has a defined sexual life cycle, the sexual cycle of *Coccidioides* is unknown (Sigler et al. 1998). However, typical ascomycete mating-type (*MAT*) loci were identified in *Coccidioides* using comparative genomics methods (Mandel et al. 2007; Fraser et al. 2007). *MAT1-1* and *MAT1-2* are present in a 1:1 Mendelian ratio in over 400 strains of *Coccidioides immitis* and *C. posadasii*, which suggests the sexual recombination is frequent in these species (Mandel et al. 2007). Moreover,

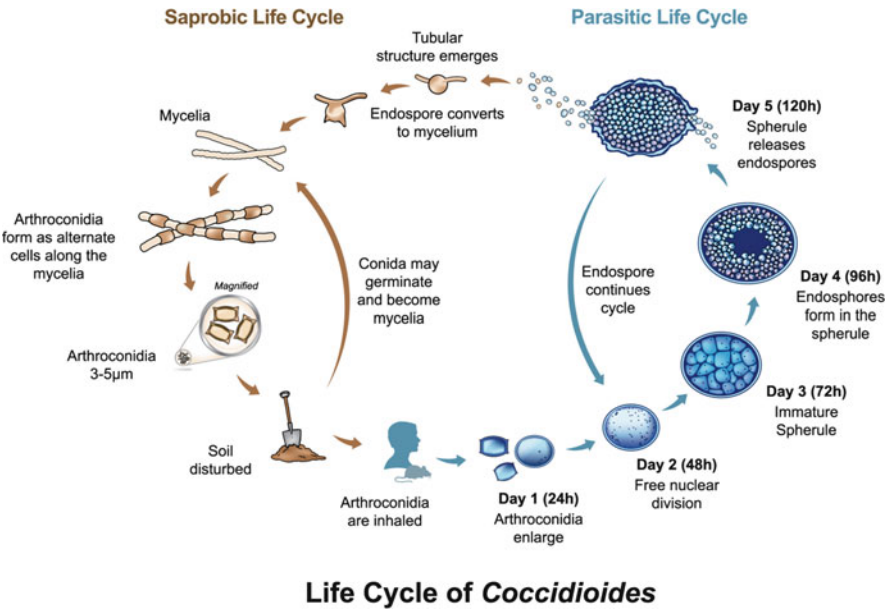


**Fig. 4.1** Dimorphic asexual life cycle of *Coccidioides*. From Lewis et al. 2015, used with attribution

mRNA is transcribed for genes in the *MAT* locus, which supports the hypothesis of a functional sexual cycle. All data obtained to date are consistent with the prediction that both species of *Coccidioides* are highly recombining sexual organisms (Burt et al. 1996; Engelthaler et al. 2015).

## 4.3 Coccidioidomycosis

All work with *Coccidioides* organism requires a biosafety-level 3 containment, primarily because infectious particles are easily produced and aerosolized (Stevens et al. 2009). The organism was previously designated as a select agent but was removed in 2012 (Oct 5 2012 Federal Register; Dixon 2001). Healthy dogs, humans, or other mammals living in or visiting endemic areas can easily become infected (Cairns et al. 2000; Nguyen et al. 2013). It is thought that approximately 60% of infections are asymptomatic based on conversion data from skin testing new military recruits from non-endemic areas that were stationed in Arizona and California (Drips and Smith 1964; Smith et al. 1956). This has been supported by new data collected from skin testing prisoners in California with the delayed hypersensitivity-based skin test now commercially available (Wack et al. 2015; de Perio et al. 2015).

In Arizona and California, an increase in coccidioidomycosis (CM) has been reported since 1995 (Thompson et al. 2015; Twarog and Thompson 2015). Because CM severity is so variable, not all infections are diagnosed and reported, and the

overall infection rate is closer to 200,000 per year in the USA (Nguyen et al. 2013; Galgiani 2007). Mild CM in humans presents with general symptoms, such as coughing, fever, and malaise. Indeed, many community-acquired pneumonias caused by *Coccidioides* in endemic regions are misdiagnosed as viral or bacterial pneumonia (Valdivia et al. 2006). Normally, acute disease is self-limiting and antifungal therapy is not necessary. However, some of these patients can experience symptoms for many months, and medical intervention may be recommended (Chen et al. 2011; Sunenshine et al. 2007). Although severe disease manifests in less than 5% of cases, it can result in life-threatening disease, which may require surgery, antifungal drug therapy, and hospitalization (Sondermeyer et al. 2013; Flaherman et al. 2007; Galgiani 2007).

Variable exposures could also play a role in differential severity of CM. Infectious dosages of 50 arthroconidia of a highly virulent strain have an $LD_{50}$ of 17 days in a murine model of CM (Sorensen et al. 1999; Kirkland and Fierer 1983). The infectious dose of arthroconidia administered to cattle determined the level of infection (Reed 1960). Dogs infected with between $10^6$ and $10^4$ conidia died or had severe disease; whereas infection with $10^3$ conidia resulted in mild CM (Hugenholtz et al. 1958). Similarly, monkeys exposed to $10^4$ conidia had 80% fatality, and infection with 50 conidia produced nonfatal infection (Converse et al. 1962b).

In addition to infectious dose, phenotypic variation among isolates of *Coccidioides* may play a role in CM disease progression. Strain morphology varies from floccus non-pigmented to flat glabrous pigmented colonies, which suggests that the strains may produce different secondary metabolites (Baker et al. 1943). In one classic study, arthroconidia production was assessed in 47 strains (Friedman et al. 1953). The majority had typical 3–5 μm barrel-shaped arthroconidia; however, the number of conidia produced was highly variable. Growth media type affected this phenotype: some strains grown on glucose yeast extract produced conidia, but not on Sabouraud's agar, and vice versa. Three strains produced no conidia on either media. This variation in conidial production could result in variable host exposure.

Variation in virulence has been described (Friedman and Smith 1957; Berman et al. 1956; Friedman et al. 1955; Huppert et al. 1967). Three human clinical strains' $LD_{50}$ values ranged from 17 to 90 days after infection with 100 arthroconidia (Friedman et al. 1955). The same group further assessed 27 clinical isolates with average $LD_{50}$ from 17 to 41 days; however, 10 strains did not reach an $LD_{50}$ after 90 days (Berman et al. 1956). Upon necropsy, mice showed infection for four of the nonfatal strains, but the mice did not exhibit outward signs of illness. Interestingly, one of the four strains was obtained from a fatal human infection. This strain was reassessed and showed similar virulence results. Additionally, the strain did not produce typical $3 \times 5$ micron arthroconidia and produced fewer conidia than other "normal" strains (Friedman and Smith 1957).

## 4.4 Epidemiology of Human and Animal Coccidioidomycosis

In the 1940s, one of the first investigations into the source of infection for a localized outbreak of CM was conducted (Davis et al. 1942). In April 1940 on a field trip to San Benito County, California, several Stanford students and faculty spent 2 days collection specimens and camping. Ten days after return to campus, a student was seen at the health center with fever, chest congestion, and malaise. Five more students from the same field trip reported similar illness within the week. Although the other students recovered, the first student that had become ill was diagnosed with coccidioidomycosis. Eventually, the group exposure was determined to the result of students digging a rattlesnake out of ground squirrel burrow. *Coccidioides immitis* was cultured out of the soils that were collected at the presumed exposure site.

Phylogenomic analyses reveal that *C. immitis* and *C. posadasii* speciated between five and ten million years ago (Engelthaler et al. 2015; Sharpton et al. 2009). The genus *Coccidioides* is possibly as old as 40–50 million years (Bowman et al. 1992; Fisher et al. 2002). Many mammalian orders rapidly diversified during the early Cenozoic, and the appearance of rodent fossils in North America corresponds to the proposed emergence of the *Coccidioides* genus (Fisher et al. 2002; Tapaltsyan et al. 2015; Saarinen et al. 2014). The emergence of both the Sierra Madres and Rocky Mountains in North America corresponds with divergence among early North American mammals (Saarinen et al. 2014; Bally and Palmer 1989). As South America was a separate continent until approximately three million years ago, recent introduction of *Coccidioides posadasii* to that region, and the origin of *Coccidioides* in the Sonoran Desert, is supported by both genomics and geological records (Engelthaler et al. 2015).

### 4.4.1 Climate

Climate clearly influences the incidence of CM and presence of the organism in the environment. Early investigations into the role of climate at Williams Air Force Base in Maricopa County during WW2 showed two seasonal increases in infection rates after winter and summer precipitation (Hugenholtz 1957). A similar trend among Arizona residents has been observed more recently (Tamerius and Comrie 2011; Kolivras and Comrie 2003). In Kern County California, only a single increase in infection rate occurs after the winter rainy season (Talamantes et al. 2007). Climatic factors that might affect rates in other endemic area, specifically in Mexico and South America, are unknown at this time (Vargas-Gastelum et al. 2015; Baptista-Rosas et al. 2007, 2012). The recent autochthonous infections in Washington state raise concerns, as there is not a consensus on the effect climate change will have on the spread of the organism into new areas (Litvintseva et al. 2015). The fungus has been found sporadically at Dinosaur National Monument in northern Utah, which indicates suitable habitat can be found in the Great Basin Desert (Johnson et al. 2014; Fisher et al. 2007; Petersen et al. 2004). Climate change predicts less frequent but more intense precipitation, and higher mean temperatures in the western USA, which may expand the endemic region.

### 4.4.2 Environmental Niche

Current understanding of the distribution of the fungus in the environment is based on extensive skin testing using a delayed-type hypersensitive reaction to various *Coccidioides* antigens (Fiese 1958). Using either spherulin (antigen derived from parasitic growth phase) or coccidioidin (antigens derived from saprobic growth phase), researchers mapped highest disease prevalence in the southwestern USA (Pappagianis 1988; Ajello 1971). Long-term Arizona residents in Maricopa County (Phoenix), Pima County (Tucson), and Pinal County (Casa Grande, Florence) had over 70% positive skin test rates, when compared to surrounding counties with only 10–40% reactivity rates (Maddy 1957, 1958b; Palmer et al. 1957; Edwards and Palmer 1957). Similar testing completed in California shows that Kern County (Bakersfield), Tulare County (Visalia), and Kings County (Hanford) residents had 50–70% skin test positive rates, while in surrounding counties positive skin tests dropped to 10% (Edwards and Palmer 1957). Additionally, in Mexico, Central America, and South America, similar distributions of positive skin tests have been found (Campins 1970; Mayorga and Espinoza 1970). However, in sparsely populated regions, this approach may not reflect the distribution of *Coccidioides* in the environment. Moreover, human migration over large and small spatial scales confounds fine spatial-scale analyses.

Several groups have worked to understand the ecology of *Coccidioides* (Whiston and Taylor 2014; Barker et al. 2012; Baptista-Rosas et al. 2007; Lacy and Swatek 1974; Swatek and Omieczynski 1970; Teel et al. 1970; Elconin et al. 1964). Defining factors that determine the presence of *Coccidioides*, as well as distribution of the fungus in the soil at local sites, has been investigated (Litvintseva et al. 2015; Johnson et al. 2014; Barker et al. 2012; Baptista-Rosas et al. 2007, 2012; Kolivras and Comrie 2003; Greene et al. 2000; Lacy and Swatek 1974; Swatek 1970; Swatek and Omieczynski 1970; Egeberg and Ely 1956). Environmental isolates of *Coccidioides* are usually obtained via inoculation of soil extracts in a susceptible rodent model (Davis et al. 1942; Levine and Winn 1964). The distribution of the fungus in the environment has been determined to be sporadic and highly localized, on the order of a square meter or less in area (Maddy 1958b, 1965). Additionally, trapping of rodents at the positive sites was conducted, with low overall levels of infectivity (Emmons 1942, 1943; Emmons and Ashburn 1942).

Defining key factors that explain presence of *Coccidioides* in the environment remains an elusive problem. Associations with saline and alkaline soils are the pattern in California (Plunkett et al. 1963; Egeberg et al. 1964; Elconin et al. 1964). However, in Arizona sandy and porous soil along with rodent burrows appears to be the strongest association (Barker et al. 2012; Emmons 1942; Maddy 1959, 1965; Smith 1971; Swatek 1970). However, caution is warranted when attempting to generalize the results, due to few studies and variable design of collection. Overall, most soil samples tested are negative (ranges from 99 to 80%), and completely randomized sampling approaches have resulted in predominately negative results (Lacy and Swatek 1974; Greene et al. 2000; Lauer et al. 2012;

Barker et al. 2012; Baptista-Rosas et al. 2012). Complex relationships among microbial organisms that share the same habitats have been investigated (Egeberg et al. 1964; Orr 1968). Direct plating from soil often results in overgrowth by more rapidly growing fungi under laboratory growth conditions (Swatek and Omieczynski 1970; Greene et al. 2000; Barker et al. 2012). However, *Coccidioides* is competitive under certain circumstances and may persist for decades the same location (Barker et al. 2012; Greene et al. 2000).

Distinct population and species boundaries, both within and among each species, are still unclear due to evidence of hybridization and introgression and that both species have been recovered among patients in southern California and northern Mexico (Neafsey et al. 2010; Fisher et al. 2001, 2002; Canteros et al. 2015; Johnson et al. 2014; Litvintseva et al. 2015; Lauer et al. 2012). MLST analysis of over 600 clinical and environmental isolates reveals population structure within Arizona and that clinical isolates are distinct from environmental isolates (Teixeira and Barker 2016).

Additionally, techniques to detect the fungus in the environment are being developed, which will help to understand and define the environmental niche of *Coccidioides*. New work on air sampling has provided a needed tool to monitor seasonal fluctuations (Chow et al. 2016). Extracting DNA from soil and dust has become much more common and molecular methods to detect the organism more robust (Johnson et al. 2014; Lauer et al. 2012; Baptista-Rosas et al. 2012; Litvintseva et al. 2015). Although detecting *Coccidioides* DNA in soil does not prove the presence of infectious arthroconidia, it is a method for screening a large number of soil samples, which would be necessary to model the environmental niche of the fungus.

### 4.4.3 Substrate Preferences

Comparative genomic studies have revealed functional differences associated with pathogenic, saprobic, or commensal lifestyles. *Coccidioides* species can digest keratin and other animal products and appear to have lost many genes associated with plant-derived carbon sources (Whiston and Taylor 2014, 2015; Sharpton et al. 2008). This suggests that this genus has specialized on animal-derived nutrients. This could be either acquired from tissue digestion during the parasitic phase in vivo or could be dead, decaying, or other sources of keratin such as skin, feathers, and hair (Lange et al. 2016; Lopes et al. 2008). It is likely that the primary nutritional mode is closely associated with animal-derived sources and may have led to the evolution of the parasitic lifestyle (Whiston and Taylor 2014; Sharpton et al. 2009).

Specifically, comparisons between *Onygenales* and *Eurotiales* (sister orders) show a reduction of cellulose-binding domain containing proteins, tannases, cellulases, cutinases, melibiases, pectin lyase, and pectin esterases among the *Onygenales* (Sharpton et al. 2009). These are all classes of genes associated with

plant-derived nutritional sources. Two families appear to be expanded only in *Coccidioides*, and in particular the M35 class of deuterolysin metalloproteases, which contains at least one known virulence factor Mep1 (Hung et al. 2005; Whiston and Taylor 2015). This family of proteases has a preferred substrate of histones and protamines, which are arginine-rich molecules (Doi et al. 2003). This class is also under positive selection, supporting the idea that these genes are associated with the evolution of *Coccidioides* (Li et al. 2012). It is suggested that keratin degradation is associated with M35 class of metalloproteases, and thus *Coccidioides* may be associated preferentially with animal-derived nutritional sources, rather than plant-derived nutrients. This remains to be experimentally proven, and it is possible that the role of M35 deuterolysin metalloproteases in *Coccidioides* has diverged into new, and as yet unexplored, functions.

Other animal-associated nutrition sources include dung and frass. Fecal samples taken from lizards (*Uta stansburiana*, *Gerrhonotus* spp., *Sceloporus occidentalis*, *Crotaphytus wislizeni*, *Cnemidophorus tigris*), skunks (*Spilogale gracilis*), black-tailed deer (*Dama hemionus*), goats (*Capra* spp.), sheep (*Ovis* spp.), and burros (*Equus asinus*) near positive soil locations were subjected to culture to attempt to recover *Coccidioides*; however, none grew the organism (Swatek et al. 1967). *Coccidioides* has been cultured from bat guano in a single report (Krutzsch and Watson 1978).

### 4.4.4 Range Expansion

*Coccidioides* spp. are found in arid or semi-arid regions throughout the Americas but are thought to be at highest prevalence in southern Arizona (Fig. 4.2) (Fisher et al. 2007). *C. immitis* is found in central and southern California (Fisher et al. 2001). The range extends into northern Mexico, and recent work has found *C. immitis* in Yakima and Benton counties of Washington, at Dinosaur National Monument in Utah, and from a patient in Colombia with no travel history (Marsden-Haug et al. 2014; Litvintseva et al. 2015; Johnson et al. 2014; Canteros et al. 2015). *Coccidioides posadasii* is found in Arizona, Nevada, Utah, New Mexico, Texas, and throughout Mexico, with dispersed populations in Central and South America (Whiston and Taylor 2014; Duarte-Escalante et al. 2013; Brilhante et al. 2013; Campins 1970). Hybrid strains indicate that the two species coexist in nature (Neafsey et al. 2010). To determine if this is a recent or ancient phenomenon, environmental sampling is needed to accurately assess the prevalence of both species, and hybrid offspring, at a given location.

Direct isolations from soil throughout the range of both species in North and South America will clarify population structure and species boundaries. Clinical isolates are still needed to track emergence of any virulent strains or new point source outbreaks (Litvintseva et al. 2015). With greater surveillance and awareness, it is predicted that potential habitat for and cases of *Coccidioides* may be found throughout the western USA (Baddley et al. 2011). In fact, recent reports of cases in


**Fig. 4.2** Distribution and prevalence of *Coccidioides* spp. in arid or semi-arid regions throughout the America

Missouri northeast of the endemic area are concerning (Turabelidze et al. 2015). Although many of these cases could be the result of travel to endemic areas, the possibility must be considered that these are locally acquired infections as a result of drier soil and dust storms, fomites, or even unrecognized small foci of growth of the fungus (Hage et al. 2012; Stagliano et al. 2007; Desai et al. 2001).

## 4.5 Pathophysiology and Clinical Signs of Coccidioidomycosis

Both *Coccidioides* species cause the disease coccidioidomycosis (CM) also referred to as San Joaquin Valley fever, valley fever, desert rheumatism, or "cocci/coccy."

Nonfatal disease after exposure opened the possibility of vaccine development (Levine et al. 1965; Converse et al. 1962a; Swatek 1970). Starting in 1960s, the first vaccine was made with killed spherules (Levine and Kong 1965, 1966; Levine et al. 1965; Converse 1965; Castleberry et al. 1965). Unfortunately, severe side effects and lack of significant protection at the dosage given complicated further development of the killed vaccine (Pappagianis 1993). Work continues to identify candidates for vaccine development (Yoon and Clemons 2013; Hung et al. 2012; Cole et al. 2012; Xue et al. 2009; Awasthi 2007; Johnson et al. 2007; Awasthi et al. 2005). The development of an effective vaccine would provide needed protection to anyone in endemic areas (Nguyen et al. 2013; Cole et al. 2012).

Prior to the 1950s, there was no effective treatment for coccidioidomycosis (Einstein 1975). The first drug to be found effective was Amphotericin B; however, long-term treatment is complicated by nephrotoxic side effects (Longley and Mendenhall 1960; Fiese 1957; Halde et al. 1957; Lawrence and Hoeprich 1976). The current recommended treatment of CM is fluconazole (Catanzaro et al. 1990; Fierer et al. 1990; Galgiani et al. 1988; Finquelievich et al. 1988; Stevens 1977). Although these drugs are generally well-tolerated, toxicity and drug interactions are still concerns (Stevens and Clemons 2007). Even with treatment, infections may not be cleared for patients who have disseminated disease, although recent work with nikkomycin Z shows promise (Shubitz et al. 2013; Galgiani 2007; Hector et al. 1990). Frequently, lifelong therapeutics and monitoring of disease are required, particularly with coccidioidal meningitis (Antony et al. 2006).

Otherwise healthy people and animals living in or visiting endemic areas contract CM via the inhalation of conidia. Rarely, infection has occurred by dermal invasion, in laboratory accidents, and from bandaged subcutaneous lesions (Gaidici and Saubolle 2009; Smith and Harrell 1948; Fischer and Kane 1973). Although most human infections are asymptomatic, symptoms can range from mild to severe (Nguyen et al. 2013). It is argued that the primary reason for this variation is host genotype (Galgiani 2014). This is an inherently unsatisfying argument, given variation in disease presentation as a result of both inoculum levels, as well as isolate/strain virulence in various laboratory models of infection (Cox and Magee 1998, 2004; Cox and Vivas 1977; Hugenholtz et al. 1958; Friedman and Smith 1957; Berman et al. 1956; Friedman et al. 1953, 1955). Infectious dose, variation among strains, and variation among hosts all play a role in disease outcome. Genome-wide association studies (GWAS) could define genetic-based differences in fungal virulence and host response (Muller et al. 2011). Additionally, defining conditions that influence *Coccidioides'* growth and reproduction will assist with preventing exposure.

### 4.5.1 Coccidioidomycosis in Primates

Progression and severity of disease in humans are influenced by host response to infection. An increase in disease burden has been detected as an increasing number of naïve hosts travel to endemic areas (Fig. 4.3). North American census data shows

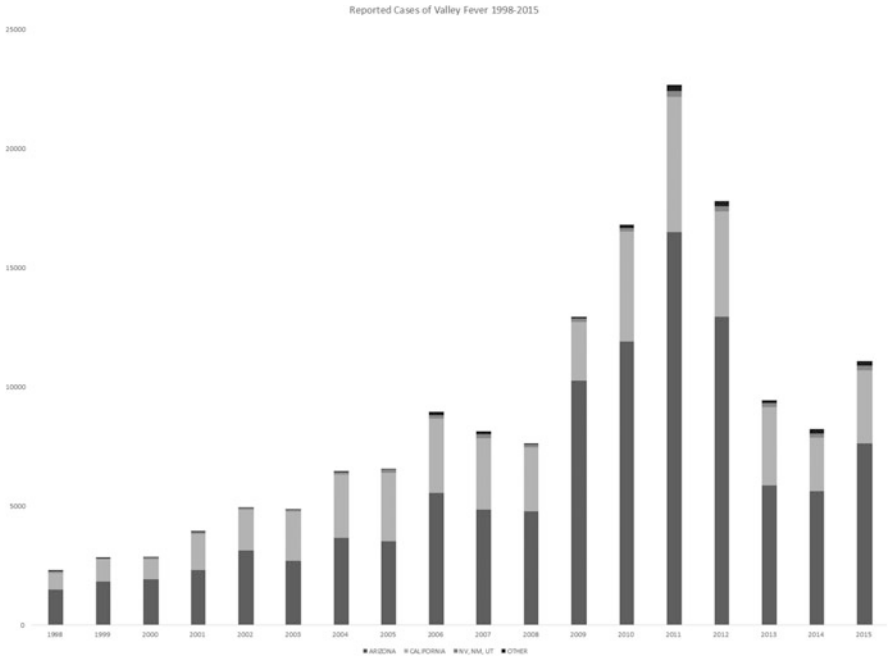


**Fig. 4.3** Reported cases of coccidioidomycosis in the USA between 1998 and 2015. Data retrieved from https://www.cdc.gov/fungal/diseases/coccidioidomycosis/statistics.html

Arizona population has increased from 3,665,228 in 1990 to 6,731,484 in 2014, with a median age of 36.5 and around one million people aged 65 and older. In California population has increased over the same time period, from 29,760,021 to 38,802,500, with a median age of 35.6 and 4,617,907 over 65. Severe disease and negative outcomes are more common in elderly vs. younger patients (Blair et al. 2008). Persons with underlying disease such as HIV infection or diabetes can have greater risk of disseminated infections (Ampel 2007; Wheeler et al. 2015) The third trimester of pregnancy is a risk factor for disseminated CM (Crum and Ballon-Landa 2006). Transplant patients are at risk of severe disease, and antifungal prophylactic therapy and screening for patients in the endemic area is recommended (Mendoza et al. 2015; Kahn et al. 2015; Kauffman et al. 2014). Additionally, there is an indication that certain ethnicities have more severe disease and higher rates of dissemination, specifically African Americans (Wheeler et al. 2015; Ruddy et al. 2011; Pappagianis et al. 1979; Sievers 1974). Finally, certain professions or living conditions may expose people to higher inoculum, such as construction, landscaping and living in rural dusty areas (Yau 2016; Das et al. 2012; Cowper and Emmett 1953; Sievers and Fisher 1982).

Among genetic determinants associated with higher possibility of dissemination are mutations in STAT1, STAT3, IL-12Rβ-1, and IFN-γR1. The STAT1 mutation conferred a constitutively active gain of function, which likely results in a

dysregulation of IFN-γ mediated inflammation, and was associated with both severe CM and histoplasmosis infections (Sampaio et al. 2013). The STAT3 mutations associated with Job's syndrome result in hyper-IgE levels in serum and dysregulation of IL-17 and Th17 response to infection, and patients are at risk of severe fungal infections (Odio et al. 2015). IL-12Rβ-1 novel missense mutations in two patients with disseminated infection reveals the importance of the IL12:IL23:IFNγ intersection as a risk factor in the human host for severe disease (Vinh et al. 2011). Finally an IFNγ receptor 1 autosomal dominant mutation resulted in severe and long-term disease in a pediatric case of CM, culminating to a coinfection with nontuberculosis *Mycobacterium* (Vinh et al. 2009). Upon determination of the root cause of the susceptibility and aggressive antimicrobial treatment, the patient improved.

These limited but important studies highlight the axis of IL12:IL23:IFNγ deficiencies and dysregulation as one cause of severe disseminated CM in humans. However, it does not explain a majority of cases or the cause of severe acute disease. These studies remain to be completed, and highlight needed future work. In addition, nonhuman primates are susceptible to infection, and several documented cases of captive macaques, chimpanzees, and baboons have been reported (Johnson et al. 1998; Bellini et al. 1991; Rosenberg et al. 1984; Rapley and Long 1974; Hoffman et al. 2007; Herrin et al. 2005; Ginocchio et al. 2013; Beaman et al. 1980; Breznock et al. 1975; Blundell et al. 1961). These reported infections are frequently severe disseminated valley fever; however it is not known if this is a common manifestation of the disease in nonhuman primates and how this informs us about human disease. Certainly, primates have been used in vaccine research, and immune profiles have been observed when compared to humans.

### 4.5.2 Coccidioidomycosis in Dogs

Domestic dogs (*Canis familiaris*) have been proposed as sentinels of disease and a way to map the organism in the environment in endemic regions where the disease is not reported to the CDC or occurrence outside the endemic region (Gautam et al. 2013). The approach has had success in California and Arizona and has been useful in guiding environmental collections of *Coccidioides* (Barker et al. 2012; Shubitz 2007; Butkiewicz et al. 2005; Shubitz et al. 2005; Grayzel et al. 2016). Canine prevalence data would be a useful tool for monitoring emergence of new regions of endemicity.

Certain breeds may have higher risk of disseminated disease. Data currently are more suggestive than definitive. Early work that studied 100 dogs postmortem found that male dogs, boxers, and Doberman pinschers had higher prevalence of severe disease that resulted in death (Maddy 1958a). A more recent study showed that boxers, beagles, pointers, Australian shepherds, and Scottish terriers were over-represented in comparison to general population in a retrospective study of 218 dogs based in Davis, California (Davidson and Pappagianis 1994). A prospective study on 124 dogs and a cross-sectional study of 381 dogs in Arizona grouped

dogs according to American Kennel Club guidelines and found no association with breed group (Butkiewicz et al. 2005). Major impediments to understanding breed specificity are changing breed popularity, unknown pedigrees, and lack of reliable demographic data. Certain breeds of dogs tend to be more popular and are thus more likely to have high incidence within a single clinic. Backyard breeders and unreliable pedigrees can confound the correct breed assignment. Finally, demographic data currently relies on owners licensing dogs, and for certain breeds that are deemed dangerous (pit bulls, German shepherds, Rottweilers, etc.), the breed may not be disclosed (i.e., listed as "mix" or "unknown").

Conversion to a positive serology in dogs occurs at a similar rate compared to humans: around 70% of infections are asymptomatic (Shubitz et al. 2005). Approximately 24% of 124 dogs enrolled in a prospective study that were followed for 2 years converted positive for *Coccidioides* exposure, with 6% having clinical disease (Butkiewicz et al. 2005). Another benefit to using naturally infected dogs as models to understand disease in humans is that severity and disease manifestations are similar. The disease generally stays localized to the lungs and hilar lymph nodes (Graupmann-Kuzma et al. 2008). Dogs can develop extrapulmonary complications, such as dissemination to bone, meninges, and other internal organs in about 20% of symptomatic cases, which is higher than in humans (Davidson and Pappagianis 1994).

Treatment options are similar to what is available for people. Amphotericin B and azoles are the drugs of choice with similar toxicities and side effects. Generally, it is recommended that any animal that is clinically ill should be treated with antifungals (Graupmann-Kuzma et al. 2008). Diagnosis is often based on clinical manifestations consistent with disease combined with serological testing, travel history, and radiographic findings (Shubitz and Dial 2005; Ajithdoss et al. 2011). The decision on ending antifungal treatment is also complicated by the fact that in some animals IgG titers do not drop below the threshold that would allow a determination of a cure or remission and lifelong antifungal therapy is common for dogs with disseminated disease (Graupmann-Kuzma et al. 2008). New antifungals, such as nikkomycin Z, are being developed and show efficacy in dogs (Shubitz et al. 2013, 2015).

Other canids that live in endemic regions that may be naturally infected include Mexican gray wolves (*Canis lupus baileyi*), coyotes (*Canis latrans*), kit foxes (*Vulpes macrotis*), and the endangered San Joaquin kit fox (*Vulpes macrotis mutica*). A standard method of testing wild animals for any infectious disease is blood collection, which is followed by serological analysis. For CM, an antibody immunodiffusion assay or ELISA to detect *Coccidioides* + IgG or +IgM is standard. However, a negative result may be uninformative, and certainly in wild animals where testing has not been optimized, results should be viewed with caution. No reports of valley fever in wolves were found in the literature; however, wolves were eliminated from most of the endemic region prior to awareness of the disease and were not likely residents of lower deserts (Carroll et al. 2014). One report of an investigation of valley fever among coyotes reveals that three of five coyotes captured in the Tucson AZ area were subclinically infected and two had culturable fungus from tracheobronchial lymph node tissue (Straub et al. 1961). The fungi were

then tested in a mouse model, and only one of the two cultures produced an infection consistent with valley fever. Finally, a survey of San Joaquin kit foxes showed a very low level of positive *Coccidioides* serology; however, the exact testing method was not reported (McCue and O'Farrell 1988).

A greater understanding of disease prevalence and severity among all canids found in endemic regions could provide valuable information on the genetic basis of host response to disease and distribution in the environment.

### 4.5.3 Coccidioidomycosis in Cats

The prevalence of valley fever in domestic cats (*Felis catus*) and other felines is thought to be lower than canines and with a very different presentation (Greene and Troy 1995). An interesting case presentation was reported in a wild mountain lion (*Felis concolor*) that had been trapped in Texas and transported to Florida for research purposes related to Florida panther reintroduction (Clyde et al. 1990). The animal was otherwise healthy; however, lung function and blood work were identified as abnormal during an examination and minor surgery. A communicable disease needed to be rapidly diagnosed as other mountain lions were to be released into the wild, and this animal had been in proximity to them. The animal was euthanized, and upon postmortem examination, disseminated CM with peritoneal involvement was discovered and likely represented a natural infection in a wild animal. Another peritoneal CM in a mountain lion was reported in a captured animal taking up residence in a tree in a private yard in Kern County, California (Adaska 1999). The animal was extremely lethargic and emaciated. Recent reports of plague in the area were cause for concern, and the animal was shot. Postmortem examination revealed several granulomatous structures throughout the peritoneum consistent with *Coccidioides* spherules. Infection was confirmed via histopathology and culture.

Other large felids in captivity have been reported infected by *Coccidioides* including a Indochinese tiger in the El Paso Zoo (*Panthera tigris corbetti*) and two Bengal tigers (*Panthera tigris tigris*) (Helmick et al. 2006; Henrickson and Biberstein 1972). In the case of the tiger, other animals tested at the facility did not have positive serology, and few cases of valley fever had been detected at the facility. The tiger had other comorbidities: chronic renal disease and pancreatic adenocarcinoma (Helmick et al. 2006). The other case report detailed that both Bengal tigers were male and contained at the same location in southern California. The tigers also had severe hepatic disease, which may have predisposed them to disseminated CM. In these two cases, infection with *Coccidioides* may have been asymptomatic for several years and only surfaced when other disease processes occurred.

In domestic cats, valley fever has variable presentation with the first report of disease in two cats appearing in 1963 (Reed et al. 1963). Both animals were euthanized and upon necropsy confirmed to have significant disseminated CM and disease manifestations similar to canine. However, cats are thought to have fewer

fungal infections, and few reports of feline CM are found in the literature. Cats tend to be diagnosed with valley fever later in life, with an average age of 6.2 years at diagnosis, and the most common clinical manifestation was skin involvement (Greene and Troy 1995). This study of 48 cats also revealed that respiratory distress was not common. The primary treatment was ketoconazole; however fluconazole or itraconazole was also used. In 44 of the 48 cats treated, 25% failed treatment and were euthanized or died soon after diagnosis. Of the remaining, long-term (10 months) therapy was necessary with relapse after removal from treatment in a few cats.

### 4.5.4 Coccidioidomycosis in Armadillos

In South America, CM outbreaks have been associated with armadillo hunters (Eulalio et al. 2001; Wanke et al. 1999). Armadillos have lower body temperature than many other mammals and harbor other pathogens, primarily *Mycobacterium leprae*, the causative agent of leprosy (Duthie et al. 2011; Loughry et al. 2009). An investigation of 26 captured armadillos (*Dasypus novemcinctus*) revealed that three were subclinically infected. No evidence of gross pathology or histopathology was discovered upon necropsy; however, macerated spleen and lung tissue grew colonies consistent with *Coccidioides*. These colonies were subsequently used to infect mice, and these mice developed CM.

The role of armadillos in the ecology, distribution, and prevalence of *Coccidioides posadasii* in the environment is unknown. These animals have been implicated in association with another fungal disease, paracoccidioidomycosis (Bagagli et al. 2006; Arantes et al. 2016). Additionally, whether or not this association is restricted to South America, or also occurs in Texas, remains to be assessed. An interesting observation however, is the fact that Texas and South America fungal isolates are more genotypically related than Texas isolates are to Arizona isolates, despite being geographically more distant. Armadillos are not found commonly in Arizona and Central California.

### 4.5.5 Coccidioidomycosis in Rodents

The role of desert rodents, specifically the Heteromyidae, in the life cycle of *Coccidioides* is an area of research that has provided confusing data. Early researchers noticed a correlation of higher rates of infection with soil disturbance around rodent burrows (Emmons 1942; Stiles and Davis 1942), which suggests a rodent reservoir for *Coccidioides* (Ashburn and Emmons 1942). Trapping of 1942 animals occurred in Lordsburg, NM, and Wilcox, Tucson, Casa Grande, and Phoenix AZ. A range of species were obtained, including pocket mice, kangaroo rats, grasshopper mice, deer mice, pack rats, ground squirrels, rabbits, and harvest mice. No animals from Lordsburg or Wilcox were infected with *Coccidioides*. Even in Tucson, Phoenix, and Casa Grande, infection rates in trapped wild rodents were low.

Seven out of 207 animals (pocket mice and kangaroo rats only) investigated had confirmed *Coccidioides* infection, with three additional animals having lesions but no fungal growth (Emmons 1943). Wild-caught rodents are susceptible to infection by *Coccidioides*; however, route and dosage of infection did not mimic a natural infection (Swatek and Plunkett 1957). *Onygenales* fungi degrade keratin; thus it is possible that *Coccidioides* is associated with hair and skin in rodent burrows (Untereiner et al. 2004; Sharpton et al. 2009).

It is possible that a rodent is highly susceptible to CM. Because a sick rodent could be susceptible to predation, a severely ill animal may die in the burrow. Two lines of evidence support this hypothesis. Tissue from infected mice fed to predators did not produce fungal colonies from fecal or pellet material (Swatek et al. 1967), and when infected animals were sacrificed and buried in soil negative for *Coccidioides*, the soil was subsequently positive for growth (Maddy and Crecelius 1965). *Coccidioides* does not survive gut passage in foxes, coyotes, or owls (Swatek et al. 1967). Fecal samples from various predators and owl pellets were collected for 5 years near known positive soil sites, but no *Coccidioides* was recovered (Swatek and Omieczynski 1970; Swatek et al. 1967). Non-predators such as lizards, skinks, a burro, deer, goat, and sheep were also analyzed. Interestingly, *Coccidioides* does survive in the gut of laboratory and wild mice (Lubarsky and Plunkett 1954). This supports the possibility of transmission of *Coccidioides* through the gut of rodents, which frequently cannibalize.

Laboratory mice have also shown variable resistance to infection (Kirkland and Fierer 1983). Inbred mice in particular are highly susceptible to severe disease at low dosage of conidia in an intraperitoneal infection model. Comparing DBA/2N (outbred) mice to Balb/c or C57b6 (inbred) mice, the mean lethal dose for outbred was greater than $10^5$ vs. less than or equal to $10^3$ per mouse. IL-10 deficiencies have been implicated as the source of this susceptibility (Fierer 2007; Fierer et al. 1998).

### 4.5.6 Coccidioidomycosis in Captive Animals and Other Wildlife

Many wild and domestic mammals are susceptible to CM. The first report of a California sea lion (*Zalophus californianus*) infected with *Coccidioides* was a captive animal that was housed in a zoo in Tucson, AZ (Reed et al. 1976). Several years later, a naturally infected dolphin (*Tursiops truncatus*) was found upon necropsy to be infected by *C. immitis* (Reidarson et al. 1998). In a recent retrospective report, 36 wild marine mammals that had beached along the Central California coast between 1998 and 2012, including sea lions, sea otters, and harbor seals, were found to be infected with *Coccidioides* (Huckabone et al. 2015). How marine mammals are exposed remains an open question; however, it is most likely from dust and airborne particulate moving from endemic areas in California to the ocean.

Captive animals in endemic regions are a source of unusual infections but provide information about the range of susceptible hosts. A black rhinoceros (*Diceros bicornis*) that was moved from Texas to the Milwaukee County Zoo developed severe progressive lameness that was determined upon necropsy to have been caused

by disseminated CM (Wallace et al. 2009). Interestingly, between 1984 and 1994, the Phoenix Zoo had several wallabies and kangaroos infected and perish from valley fever (Reed et al. 1996). In another endemic region, a case of a giant red kangaroo being infected, as well as positive soil in its enclosure, was also reported (Hutchinson et al. 1973). One recent case of a koala at the San Diego Zoo succumbing to infection was also reported (Burgdorf-Moisuk et al. 2012). Whether marsupials are particularly susceptible to severe disease remains unknown.

Other reported wildlife native to the Sonoran Desert that has been found to be naturally infected and suffer disease includes bats, desert bighorn sheep, and javelina (peccary). Bats appear to be incidentally infected by *Coccidioides* (Cordeiro Rde et al. 2012; Krutzsch and Watson 1978). In a recent survey looking for another fungus *Histoplasma capsulatum*, *Coccidioides posadasii* was discovered. An experimental infection of *Macrotus californicus* (California leaf-nosed bat) showed this animal to be susceptible to a range of dosages: 50, 100, 200, and 400 conidia (Krutzsch and Watson 1978). However, the pallid bat (*Antrozous pallidus*) was infected only at the highest dosage of 400 conidia.

In the one reported case of desert bighorn sheep (*Ovis canadensis nelsoni*), the ram, along with 12 other sheep, was captured in November 1984 from the Marble Mountains in San Bernardino County as part of a relocation effort (Jessup et al. 1989). Animals were penned over the winter in a 17-acre enclosure in the Whipple Mountains near the Colorado River. The herd was released in the February 1985. In mid-September 1985, the ram was observed to have a respiratory infection and died shortly after capture. Postmortem revealed severe disseminated CM, with lungs being heavily infected and damaged. Continued follow-up with the rest of the herd revealed no additional evidence of CM, and no other reports have appeared. Thus it is unknown how frequently this animal is infected and what the burden of disease is for this native desert dweller.

The javelina, or the collared peccary (*Pecari (Tayassu) tajacu*), is a common resident of the desert southwest and behaviorally likely to be exposed to large inocula. However, only a single report was found in this animal (Lochmiller et al. 1985). The 25 animals in the report were captured throughout Texas and housed in an outdoor enclosure at Texas A&M University. In January 1984, a female exhibited neurological symptoms that resulted in euthanasia, and a blood analysis indicated an infection. The two other animals in the same pen were also euthanized as prevention. Necropsy revealed several granulomas in the lungs, kidney, and spleen verified as *Coccidioides* via histopathology. It is unclear how the infection occurred, as the animals that were ill were harvested outside the endemic range, and Brazos County (where animals were held captive) is considered to be outside the endemic range. Of interest is that both reports occurred in 1984–1985. It is unknown if this was concurrent with particularly high level of disease in humans as well, as cases were not nationally reported before 1994.

### 4.5.7 Coccidioidomycosis in Livestock

Greater assessment of CM in livestock has been reported, likely because of potential economic impact. Reports in pigs, cattle, sheep, horses, and llamas have revealed high rates of infection with rare cases of disseminated disease, although llamas and horses appear to have more frequent severe disease than other livestock.

A first report of CM in cattle (*Bos taurus*) was in 1918, after a slaughterhouse observed infected thoracic lymph tissue and submitted the tissue to a USDA pathologist (Giltner 1918). The pathologist grew *Coccidioides* from the tissue and tested the organism in several animals: guinea pigs, rabbits, dogs, cattle, sheep, and swine. In calves, subcutaneous infection resulted in lesions at the site of infection but no apparent disease. However, intravenous inoculation resulted in rapid death and involvement of lung tissue.

Later observations by a veterinary meat inspector in Los Angeles slaughterhouses of 3173 cattle from the southwestern USA revealed a similar trend of natural infections resulting in thoracic lymph node involvement (Maddy 1954b). Between 1947 and 1951, *Coccidioides* infected 1.8% of all cattle (calves excluded), 2.9% of steers and heifers, and 7.3% of steers and heifers from San Joaquin Valley feedlots. Of interest was an assessment of animals shipped direct for slaughter from other areas. Upon arrival, 23 animals from west Texas (Amarillo, Lubbock), 36 animals from eastern New Mexico (Clovis, Tatum), 17 from southeastern Colorado (Springfield), and 4 from southern Oregon (Medford) were found to be infected. No animal had evidence of acute CM.

Skin test surveys of 11,643 range cattle in Arizona revealed a high rate of infection that overlapped with the disease prevalence and distribution seen in humans (Maddy et al. 1960a). Between 1954 and 1959, cattle in Arizona between 1 and 6 years of age were skin tested using the coccidioidin skin test developed for humans (Palmer et al. 1957; Edwards and Palmer 1957). Pinal County had the highest rate of infection with 42% of cattle being skin test positive. However, assessments made during slaughter at a southwestern feedlot reveal that although coccidioidal granulomas are visible in thoracic viscera, no other signs of disease were noted (Reed 1960). In addition, laboratory infection experiments with dosages ranging from $5 \times 10^5$ to $1.5 \times 10^6$ arthroconidia and mycelia intratracheally showed that cattle did not develop disease, with few granulomas in lungs or thoracic lymph tissue (Maddy et al. 1960b). Serological testing was not confirmatory; however infected animals did eventually convert to skin test positive using coccidioidin. Thus cattle are susceptible to infection but do not develop severe disease.

Reports of new world camelids infected and suffering disseminated valley fever are few; however, it appears that this animal does develop severe disease (Fowler et al. 1992). The first case report was a single 8-year-old female llama (*Lama glama*) with severe disease which was euthanized and upon necropsy was discovered to have disseminated valley fever (Muir and Pappagianis 1982). The rest of the herd was tested for infection using a complement fixation antibody test, and 3 of the 11 other llamas showed evidence of infection but no disease. This initial disease report was expanded in a report on 19 retrospective cases between 1981 and 1989

from California and Arizona (Fowler et al. 1992). All animals but one had disseminated valley fever with multiple affected organs. Clinical signs varied widely, with and without cough or dyspnea, and dissemination to kidney, liver, intestine, adrenal gland, and meninges. Dermal infection was more common in llamas from California, but no gender or age correlations were observed. Diagnosis in llamas is confounded by highly variable clinical presentation and lack of reliable serological testing. Only one additional recent report was found, which described ocular disease in a 7-year-old male llama, which disseminated and resulted in euthanasia (Coster et al. 2010). Of particular interest in this case is a lack of travel or residence in the endemic region. Llamas appear to have higher rate of complicated disease than other agricultural animals, but overall disease burden is not high.

CM in naturally infected sheep (*Ovis aries*) has been reported (Maddy 1954a; Beck 1929). Upon slaughter, in both cases, the animals had lesions in the mediastinal and bronchiolar lymph nodes. In the earlier case, *Coccidioides* was grown from the tissue and verified in a guinea pig model of infection (Beck 1929). In the second case, caseous lymphadenitis was suspected, which could be caused by a contagious bacterial infection common in sheep and goats, so tissue was sent for pathology (Maddy 1954a). *Coccidioides* was determined to be the causative agent, although no evidence of illness was present, and no validation was performed in a rodent model of infection. One experimental infection of sheep has been conducted (Giltner 1918). Two animals were infected, one intravenously and the other subcutaneously. Both animals appeared well nourished, and no evidence of outward disease was reported. However, the intravenous infection resulted in multiple organ involvement, and fungus grew from the liver, lymph, and lung tissue. The animal infected subcutaneously had no fungal structures in any tissue.

One experimental case of infection in a swine (*Sus scrofa*) is reported (Giltner 1918). Two animals were infected via the right marginal ear vein. Upon necropsy, miliary lung nodules and lesions in spleen and liver were observed. A single report of a young pig succumbing to infection was found (Prchal and Crecelius 1966). A survey of both young (6-month-old butcher hogs) and older (3-year-old breeding sows) animals in Tucson, Arizona, revealed no disease but many granulomatous lesions in the bronchiolar lymph nodes (Prchal and Crecelius 1966). *Coccidioides* was confirmed first by microscopy, followed by infection in mice. It appears that although animals are susceptible to infection, complicated disease rarely develops.

CM in horses (*Equus caballus*) is reported with higher frequency that other agricultural animals, possibly because the animals are often considered pets, rather than livestock. One review states that pulmonary involvement and weight loss is a common manifestation of disease, along with osteomyelitis and lesions in thoracic lymph nodes and liver (Ziemer et al. 1992). All 15 animals died or were euthanized, and treatment was not effective in the 4 animals where it was attempted. These cases were also interesting in that several of the animals resided in areas not considered to be highly endemic. Subsequent treatment of animals was more successful due to earlier diagnosis and treatment (Higgins et al. 2006). A case of a 14-day-old foal with acute CM that was euthanized due to severe disease suggests that some horses are more susceptible to infection and suffer disease as a result (Maleski et al. 2002).

Interestingly, the wild Przewalski's horse (*Equus przewalskii*) appears to be even more susceptible to severe disease than domesticated horses (*E. caballus*). These animals appear to be resistant to most common infectious disease of horses; however, they are susceptible to disseminated CM (Terio et al. 2003). Thirty Przewalski horses housed in the San Diego Wild Animal Park as part of a breeding and reintroduction program died over a 16-year period, with 10 deaths attributed to CM. No other exotic equids at the same facility had reported valley fever deaths. The cause of susceptibility to valley fever could be from a defect in *Coccidioides*-specific immune response, but results were inconclusive.

Specific non-mammalian hosts infected intraperitoneally, including crayfish, goldfish, and amphibians, developed mycelia in various tissues, and lizards can develop spherules in the lung (Swatek and Plunkett 1957). A naturally infected Sonoran gopher snake with pulmonary lesions and histological and microscopic evidence of *Coccidioides* infection was reported (Timm et al. 1988). Although morphology consistent with *Coccidioides* was observed, the fungus was not validated by mouse infection, and genotyping was not yet available. A second case of an infected Sonoran lyre snake at the Phoenix Zoo suggests that natural infection of reptiles deserves more attention (Reed et al. 1996). Again microscopy consistent with *Coccidioides* was observed, but in this case the fungal agent was confirmed by infection in a mouse. An incidental finding of a lung granuloma in a Gila monster was reported by the Arizona Veterinary Diagnostic Laboratory, but the animal perished from another cause (Reed et al. 1996).

No avian species have been reported to have infection. No detailed investigation of invertebrate associations, such as nematodes in soil or soil-burrowing insects, has been conducted. An interesting account of mice injected with chromium-51 and buried in soil was relayed at an international CM meeting (Egeberg 1985). Following the movement of the radiation, insects were implicated in the digestion of mouse tissue in both cases.

## 4.6 Conclusion and Future Directions

Over the last 30 years, reported cases of valley fever have increased dramatically (Sondermeyer et al. 2013; Huang et al. 2012; Hector et al. 2011; Lewis et al. 2015; Twarog and Thompson 2015). Data show that strains recovered in a recent study of Arizona isolates were highly variable with no clonal structure; therefore, a pathogenic clone was not responsible for the rise in cases (Jewell et al. 2008). A central question regarding the increase of disease remains unanswered. Possible non-mutually exclusive causes include climate change, increased host susceptibility, and changes in reporting and awareness. Another complication is the high levels of recombination, admixture, and genetic diversity and an as yet undiscovered sexual life cycle that could produce an alternative infectious morphology: the ascospore. Genetic variation in the fungus and ability to adapt to novel hosts and colonize new environments are additional unanswered questions. The potential emergence of antifungal resistance is cause for concern, and the lack of early accurate diagnosis

and treatment recommendations for humans is troublesome. Furthermore, treatment and diagnostic development for our four-legged friends is based on clinical trials in humans. Thus, many clinicians are forced to use "wait and see" approaches to treatment. Greater research effort to understand the organisms as well as the disease is needed, particularly in response to the potential for the disease to expand into new areas.

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