# Coccidioidomycosis

*Coccidiomycosis,*
*Valley Fever,*
*San Joaquin Valley Fever,*
*Desert Rheumatism,*
*Posadas-Wernicke Disease,*
*Coccidioidal Granuloma*

**Last Updated:** June 2010

## Importance

Coccidioidomycosis is a fungal infection, almost always acquired from the environment that can affect many species of mammals and some reptiles. The fungus is endemic in the soil of the southwestern United States, Mexico, and parts of Central and South America. Its distribution is patchy, but in some "hot spots," up to 70% of the human population has been infected. Most infections in people are relatively mild or asymptomatic, but severe or fatal illness also occurs, especially in the elderly or immunocompromised. Among animals, coccidioidomycosis is common in dogs, which have a spectrum of illness similar to humans. Cases have also been reported in llamas, nonhuman primates, cats, horses, a wide variety of other domesticated or wild mammals, and a few reptiles such as snakes.

## Etiology

Coccidioidomycosis is caused by the dimorphic, soil-borne, ascomycete fungi *Coccidioides immitis* and *C. posadasii* (formerly known as the "California" and "non-California" populations of *C. immitis*). *C. immitis* and *C. posadasii* differ in some characteristics such as their tolerance to heat and salt, but no differences in their pathogenicity have been recognized.

## Geographic Distribution

*Coccidioides* spp. occur in the Western Hemisphere, at latitudes between 40ºN and 40ºS, from California to Argentina. The distribution of these organisms is patchy. They are endemic in the southwestern U.S., including Arizona (where the incidence in humans is particularly high), parts of New Mexico, Texas (west of El Paso), and the central and southern portions of California, especially the San Joaquin Valley. The endemic area extends into Mexico, and foci of infection have been detected in Central and South American countries including Argentina, Colombia, Guatemala, Honduras, Venezuela, Paraguay and Brazil.

*C. immitis* seems to be restricted to California, but it might exist in some adjacent areas of Baja California (Mexico) and Arizona. *C. posadasii* is found in the remaining regions. Whether the ranges of these two organisms overlap is not known.

## Transmission and Life Cycle

*C. immitis* and *C. posadasii* are soil saprophytes that grow in semiarid regions with sandy, alkaline soils. In their mycelial (mold) form, these organisms can grow under environmental extremes, including alkaline conditions, extreme temperatures and high salinity, that other organisms cannot tolerate; however, they compete poorly with other soil fungi and bacteria outside their usual niche. *Coccidioides* spp. are propagated by two asexual reproductive structures – arthroconidia (arthospores) and endospores.

Arthroconidia are produced by the mold form growing in the environment, and are dispersed by the wind. They germinate to form new mycelia if the environmental conditions are appropriate. Arthroconidia are also infectious for humans and animals, which are accidental hosts. In the vast majority of cases, people or animals are infected by inhalation. Aerosolization of arthroconidia increases when contaminated soil is disturbed by humans (as in an archaeological dig or construction site) or by natural causes such as earthquakes or dust storms. Epidemics can occur when heavy rains, which promote the growth of mycelia, are followed by drought and winds. Arthroconidia can also be inoculated directly into skin, bone or other tissues by penetrating objects, but this seems to be uncommon. In mares, it is possible that coccidioidal abortion results from ascending infections via the vagina. Mature arthroconidia are extremely resistant to adverse conditions, and can survive for months or years in the soil and dust. Dust-covered fomites have been suspected in cases that occur outside the endemic area, when there is no history of travel to these regions.

Inside the body (usually in the lungs), arthroconidia become spherules. As each spherule enlarges, endospores develop inside it. The spherule eventually ruptures and releases the endospores, which develop into new spherules. Endospores can also

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spread to other parts of the body in the blood or lymph, causing disseminated disease. If they reach the environment, endospores can form a new mold.

Coccidioidomycosis is ordinarily not transmitted directly between people or animals; however, there are exceptions. One person was infected during the necropsy of a horse, and another was apparently infected through broken skin while embalming a person. Recently, localized coccidioidomycosis was reported in a veterinary assistant who had been bitten by a cat. In all three cases, the infection was acquired from a person or animal with disseminated disease. Coccidioidomycosis has been reported rarely in infants after contact with infectious material in the vagina at birth. Transmission through the placenta seems to be extremely rare in people. *Coccidioides* spp. can be transmitted in transplanted organs.

## Disinfection

Although fungal agents are highly resistant to most disinfectants, halogens (such as iodine, and chlorine in the form of hypochlorite [bleach]), phenolics (such as Tek–Trol®), and quaternary ammonium compounds (Di–Quat® 10–S and Roccal®–D Plus) have proven effective against *Coccidioides* spp. Arthroconidia are resistant to dry heat, but they can be inactivated by moist heat (121°C for a minimum of 15 minutes)

# Infections in Humans

## Incubation Period

The incubation period for primary pulmonary or cutaneous coccidioidomycosis is usually one to three weeks. Disseminated disease or chronic pulmonary coccidioidomycosis can occur months or years after the initial infection.

## Clinical Signs

Coccidioidomycosis is often limited to the respiratory tract. In a small percentage of cases, the fungi disseminate to other tissues from the lungs. Uncommonly, *Coccidioides* spp. can infect tissues directly from the environment.

### *Primary pulmonary coccidioidomycosis*

Acute infections in the lungs (primary pulmonary coccidioidomycosis) can be asymptomatic or so mild that they are unrecognized. In symptomatic cases, the illness is often flu-like, with fever, fatigue, malaise, headache, sore throat, coughing and/or pleuritic chest pain. Overt signs of pneumonia may also be seen. Severe respiratory disease, with high fever, dyspnea and hypoxemia, is uncommon in healthy people, but more frequent in individuals who are immunocompromised. It may progress to acute respiratory distress syndrome or respiratory failure. Approximately 10-50% of patients with pulmonary disease develop skin lesions. An erythematous, macular rash may occur in the early stages, and hypersensitivity reactions can cause erythema nodosum or erythema multiforme. Erythema nodosum, which is characterized by tender, reddened nodules on the lower extremities, usually suggests that the prognosis is good. Milder cases of primary pulmonary coccidioidomycosis are self-limited and often resolve within a few weeks, although the fatigue may persist for weeks or months. Severe cases can be life threatening. A condition that mimics septic shock has also been reported, and has a high mortality rate.

Nodules, which are often solitary, or thin-walled cavities may persist after the resolution of pulmonary disease. They are usually an incidental finding on chest x-rays, but must be distinguished from neoplasia and tuberculosis or other granulomatous conditions. Nodules and cavitations are often asymptomatic, but coughing, chest pain and/or hemoptysis may be seen. It is also possible, though uncommon, for a cavity near the pleura to rupture and cause hydropneumothorax. Cavities may persist for years before resolving.

### *Progressive pulmonary coccidioidomycosis*

In progressive pulmonary coccidioidomycosis, the clinical signs do not resolve, but develop into chronic and progressive disease. Nodular or cavitary lesions, cavitary lung disease with fibrosis, or miliary pulmonary dissemination may be seen. Even when the lungs are extensively involved, the disease usually remains limited to the respiratory tract.

### *Disseminated coccidioidomycosis*

Disseminated coccidioidomycosis occurs in a small percentage of cases, and may develop weeks, months or years after the primary infection. It is usually acute, and can be rapidly fatal without treatment, but it may also progress more slowly with periods of remission and recurrence. The skin, regional lymph nodes, bones and joints are most often affected in humans, but virtually any tissue or organ including the visceral organs and testes may be involved. The clinical signs vary with the affected tissues. A wide variety of lesions, including nodules, papules, pustules, furuncles, verrucous (wart-like) plaques, abscesses, granulomatous lesions or ulcerations, may be seen when the fungus disseminates to the skin. The head, neck and chest are most often involved. Lymph nodes that are infected may become necrotic and ulcerate or drain. Dissemination to the musculoskeletal system can result in osteomyelitis, septic arthritis and/or synovitis. Arthritis usually affects only one joint, often a weight-bearing joint such as the knees, but it can be migratory. Subcutaneous abscesses and sinus tracts can develop near the affected bones and joints. Septic shock can also be seen.

In people, dissemination to the central nervous system (CNS) usually results in coccidioidal meningitis. The symptoms may include fever, headache and signs of meningeal irritation. Cognitive impairment or personality changes are possible, and inflammation can result in complications of vasculitis, stroke or hydrocephalus.

Untreated cases of coccidioidal meningitis almost always end in death within two years. Less often, dissemination to the CNS may result in encephalitis, mass-occupying lesions, brain abscesses or aneurysms.

### *Primary cutaneous coccidioidomycosis*

Primary cutaneous coccidioidomycosis, the result of direct inoculation into the skin, is rare. The initial lesion may be a chancriform ulcerated nodule or plaque. The infection spreads along the lymphatic vessels, and may be accompanied by regional lymphadenopathy. The lesions often heal spontaneously within a few weeks if the person is immunocompetent. Osteomyelitis can be caused by direct inoculation of the bone from a penetrating object.

### *Coccidioidomycosis in immunosuppressed individuals*

Coccidioidomycosis is more likely to be serious in immunocompromised patients, especially those who have defective cell-mediated immune responses. A previous infection can also be reactivated if a person becomes immunosuppressed.

HIV-1 patients with low CD4 T cell counts are at risk for disseminated or severe coccidioidomycosis. Overwhelming pulmonary disease, which is frequently fatal, is common in this group. Patients who are less severely immunocompromised may have focal pulmonary infiltrates similar to those seen in immunocompetent patients, extrathoracic lymphadenopathy, liver disease or meningitis. Dissemination to the bones and joints does not seem to be increased in people infected with HIV-1.

The spectrum of illness in organ transplant patients is similar to coccidioidomycosis in healthy people, but the risk of disseminated or severe disease is elevated. If the organism disseminates, it may be found in multiple sites. In addition to the skin, bones, lymph nodes and meninges, other tissues such as the spleen, genitourinary system, thyroid gland, pancreas, adrenal glands, brain and transplanted organ may be involved.

## Communicability

Coccidioidomycosis is not considered to be transmissible from person to person. However, parasites found on objects in the environment, such as wound dressings, may develop into molds that form arthroconidia. Direct transmission might also be possible in rare cases. One infection, which was apparently transmitted through broken skin, occurred in a person who had embalmed an individual with disseminated disease. Neonates have been infected rarely by contact with organisms in the mother's vagina during birth.

## Diagnostic Tests

Coccidioidomycosis can be diagnosed by visualizing the parasite in respiratory secretions, pleural fluid, tissues or exudates. Organisms are rarely found in cerebrospinal fluid (CSF) in cases of meningitis. In the body, *Coccidioides* spp. form spherules, double-walled structures that vary widely in abundance and size. Most spherules are 20-80 µm in diameter, but some can be as large as 200 µm. They contain endospores, small, 2-5 µm globular structures that develop into new spherules when they are released. Spherules containing endospores are diagnostic, while spherules without endospores are presumptive evidence for coccidioidomycosis. Free endospores may occasionally be the predominant form in a specimen, and can be confused with the yeast stage of *Cryptococcus*, *Histoplasma* or *Candida*. In rare cases, *Coccidioides* spp. can form hyphae in tissues or air spaces in the lung. These cases might be misdiagnosed as carcinoma if spherules are not found. The calcofluor white (CFW) fluorescent stain, potassium hydroxide (KOH) wet mounts, Grocott-methenamine silver stain, periodic acid-Schiff stain or hematoxylin-eosin stain can be used to visualize the organism. Organisms are occasionally found with Giemsa, Papanicolau or mucicarmine stains. Gram staining does not usually detect *Coccidioides* spp.

Coccidioidomycosis can also be diagnosed by culturing affected body fluids, exudates or tissue specimens. *C. immitis* and *C. posadasii* can grow on most fungal media such as Sabouraud agar, brain–heart infusion agar, potato dextrose or potato flakes agar, with or without cycloheximide, as well as on many media used to isolate bacteria. Because these organisms do not compete well with other fungi or bacteria, samples with mixed flora should be plated onto selective as well as nonselective media. Mold colonies can usually be detected within 4-5 days, but they can appear as late as 16 days. When they first appear, the colonies are often gray and membranous and may be difficult to recognize. Older colonies are usually floccose and variable in texture. They become white or buff, but can develop other colors as they age. The hyphae are hyaline and septate. Arthroconidia are not found in young colonies, but develop as the colony ages, and can be used for presumptive identification. They tend to be barrel-shaped and are approximately 2 to 4 µm in width, thick-walled and usually multinucleated. When combined with serology, or with the detection of endospores inside spherules on direct microscopy, the presence of arthroconidia is diagnostic. Otherwise, the identity of the organism can be confirmed with a genetic probe, which recognizes *Coccidioides* spp. but does not differentiate *C. immitis* from *C. posadasii*. Older methods of colony identification, which are no longer commonly used, include immunodiffusion, propagation of the spherule phase in Converse medium, or mouse inoculation. *C. immitis* and *C. posadasii* are not easy to distinguish, but there are no apparent differences in the clinical presentation or response to treatment, and identification to the genus is often sufficient.

Coccidioidomycosis is often diagnosed by serology. Serological assays include enzyme-linked immunosorbent assays (ELISA) and immunodiffusion, which can detect both IgM and IgG, and complement fixation, which detects IgG.

A quantitative complement fixation or quantitative immunodiffusion test can be used to monitor changes in IgG titers. Specific IgM can usually be detected within 1 to 3 weeks after infection. Specific IgG can be found starting 2 to 3 weeks after exposure, but in some patients it can take several months to develop. Early cases may be seronegative, and immunocompromised patients may have poor immune responses. IgG titers are usually correlated with the severity of the infection in humans, and high or increasing titers may suggest dissemination. Patients with primary cutaneous coccidioidomycosis tend to have low IgG titers, and may be seronegative in the early stage. Titers also reflect the efficacy of treatment, as they generally decline with successful therapy. The detection of antibodies in CSF is often the only way to diagnose coccidioidal meningitis, because organisms are rarely found in this condition.

The coccidioidin or spherulin skin test was used extensively in epidemiologic studies at one time, but the reagents are no longer available in the U.S. This test indicates past as well as current infections.

Polymerase chain reaction (PCR) assays are in development.

## Morbidity and Mortality

*Coccidioides* spp. infections are common in endemic areas. Depending on the region, 10-70% of the population in the southwestern U.S. has been infected by this organism. Individuals exposed to large amounts of dust have higher infection rates. Occupational risk groups include farmers, construction workers and archaeologists. Coccidioidomycosis is seasonal, and its incidence peaks at different times in different areas, depending on the weather patterns. The number of cases increases when a wet period, followed by a dry and windy season, results in increased growth of the fungus followed by windborne dispersion of the arthrospores. Major epidemics occur intermittently, and have been associated with large earthquakes and windstorms. The incidence of coccidioidomycosis appears to be increasing in the U.S. In Arizona, the number of new cases per 100,000 population grew from approximately 12 in 1995 to 58 in 2005.

The severity of the illness is highly variable. In 60% of cases, the infection is asymptomatic or so mild that it is not recognized; the remaining 40% become mildly to severely ill. About 90% of patients have infections limited to the lungs and recover without sequelae. The remainder have residual pulmonary lesions or develop disseminated disease. Approximately 1% or less of all infections and less than 5% of symptomatic infections disseminate. The case fatality rate for disseminated coccidioidomycosis varies with the location of the organisms and the treatment. Meningitis occurs in 30-50% of patients with untreated disseminated disease, and it is almost invariably fatal without prolonged or lifelong therapy. People who have recovered from coccidioidomycosis are resistant to reinfection.

Immunocompromised persons are particularly susceptible to coccidioidomycosis. In endemic areas, this disease is common among patients who are infected with HIV-1 and have decreased CD4 T cell counts. In the only published prospective study, which was conducted in the 1980s, almost 25% of HIV-1 infected patients developed symptomatic coccidioidomycosis within approximately 3.5 years of monitoring. Better control of the HIV virus with antiretroviral drugs appears to have decreased the severity and incidence of coccidioidomycosis since that time. Other groups at increased risk for serious illness include organ transplant patients, lymphoma patients, people who are receiving long-term corticosteroids, and pregnant women, especially in the third trimester. Host genes, especially MHC class II genes, seem to be important in the risk of dissemination, and an African or Asian (especially Filipino) background increases the risk of severe illness.

## Treatment

Options for treatment range from observation to antifungal drugs, depending on the severity of the disease and risk factors for dissemination. Azoles such as fluconazole, itraconazole and ketoconazole, as well as amphotericin B, may be used. Surgical excision or debridement may occasionally be employed in disseminated cases or enlarging pulmonary cavitary lesions. Treatment may not be necessary for patients with primary coccidioidomycosis, as most cases resolve on their own and antifungal drugs can have side effects. However, some physicians recommend treatment in all symptomatic cases to decrease the duration or intensity of the illness. In some cases (such as meningitis or an infection in an HIV-1 infected patient with a low CD4 cell count), lifetime treatment may be needed to prevent relapses.

## Prevention

Coccidioidomycosis is difficult to prevent in endemic areas; however, reducing exposure to airborne dust may be helpful. Dust control measures such as paving dirt roads, seeding lawns and dampening dust with oil have been reported to decrease the number of cases in military personnel. People at risk for severe disease may, in some cases, be given prophylactic drug treatment. Transplant programs in endemic areas conduct screening programs for coccidioidomycosis. If the recipient or donor has been infected, prophylaxis or treatment may be recommended. Although vaccines are in development, no vaccine is currently available.

*Coccidioides* spp. are not normally acquired from other people or from animals. However, there are rare reports of cases transmitted in an animal bite or after contact with tissues at necropsy, and ordinary safety precautions should not be neglected. Contaminated objects that could support the growth of the mycelial form should be decontaminated or destroyed promptly, before arthrospores can form. Clinical specimens in the endemic area should be sent to a

diagnostic laboratory; in-house fungal culture is not advisable because arthroconidia from mature cultures are readily aerosolized and inhaled. Plates that are more than 3–5 days old are more likely to have arthroconidia, and are more dangerous. Biosafety level 2 practices with negative air pressure and a class II biological safety cabinet have been recommended for laboratories working with *Coccidioides* spp., but some sources suggest biosafety level 3 for all fungal laboratories.

## Infections in Animals

### Species Affected

*Coccidioides* spp. infections have been reported in many domesticated, captive exotic or wild mammals, as well as in some reptiles. Clinical cases are relatively common in dogs, llamas, nonhuman primates, and many nonnative species kept in zoos in endemic regions. They are also seen in cats and horses. Overt disease has rarely been documented in cattle, sheep or pigs, although lung lesions may be found at slaughter. Among wild animals, severe or fatal illness has been seen in sea otters, a bottlenose dolphin and cougars, and lesions have been reported in other species including coyotes, nine-banded armadillos (*Dasypus novemcinctus*) and desert rodents. *Coccidioides* spp. do not seem to affect birds.

### Incubation Period

Primary pulmonary infections usually become symptomatic one to four weeks after exposure, while disseminated disease can occur months to years later.

### Clinical Signs

*Coccidioides* spp. infections in animals vary from asymptomatic to severe and fatal. As in humans, coccidioidomycosis is primarily a respiratory disease, but in some cases, the organisms disseminate to other tissues. The most common sites of dissemination vary with the species, but nearly any tissue or organ can be affected. Involvement of the heart and/or pericardium may be more common in animals than humans, and has been reported in dogs, horses, llamas and cats. Dissemination may or may not be accompanied by signs of systemic illness.

#### *Dogs*

Many dogs may be infected subclinically. Primary pulmonary infection is the most common form in dogs that become ill. Affected animals often have a chronic cough, which may be dry, or moist and productive. Fever can be seen, but some dogs have a normal temperature. Weight loss and anorexia are common. Overt pneumonia may occur in some animals, and can be severe. Lung lesions, including solitary nodules similar to those found in humans, can be seen in some asymptomatic dogs.

Disseminated disease can occur with or without a history of respiratory illness or concurrent pulmonary signs. This form of coccidioidomycosis can develop months or years after the primary infection. The clinical signs vary with the site, and may be accompanied by nonspecific signs such as persistent or fluctuating fever, depression, anorexia and weight loss. In dogs, *Coccidioides* spp. disseminates most often to the bones, especially those of the appendicular skeleton, and causes lameness and pain. If the vertebrae are involved, there may be neurological deficits such as ataxia, paresis or paralysis, as well as back or neck pain. Draining skin nodules or tracts may be found over the sites of bone involvement. Other reported sites of dissemination include the lymph nodes, skin, subcutaneous tissues, CNS, heart, liver, spleen, kidney, eyes, testes and prostate gland. In contrast to coccidioidomycosis in humans, CNS invasion in dogs is usually characterized by granulomatous lesions rather than meningitis, and seizures are the most common sign. Involvement of the heart and pericardium may cause heart failure, arrhythmias, syncope or sudden death. Ocular lesions include fungal granulomas, anterior uveitis, iritis, retinal detachment and blindness.

#### *Cats*

There is limited information on coccidioidomycosis in cats, but skin lesions seem to be the most common presenting sign. They may appear as non-healing dermatitis, ulcers, masses, abscesses or chronic draining tracts. Regional lymphadenopathy is possible, and non-specific signs such as fever, lethargy, weight loss and anorexia are common. Severe weight loss can be the only sign in some cats. Respiratory signs are not as common in cats as they are in dogs, but many cats have lung lesions without these signs. In one series, 25% of all affected cats had respiratory distress, but coughing was uncommon. Other sites of dissemination are similar to the dog, although the bones do not seem to be involved as often. As in dogs, dissemination to the CNS usually causes granulomas; however, the clinical signs are more variable in cats, and may include incoordination, seizures, hyperesthesia, and changes in behavior. Ocular disease with anterior uveitis, iritis, fungal granulomas and/or retinal detachment may be seen. Periocular swelling and subpalpebral conjunctival inflammatory masses have been reported in some cats with ocular disease.

#### *Horses*

Relatively few cases of coccidioidomycosis in horses have been published, and most have been of disseminated disease. However, the spectrum of illness includes pulmonary disease, with or without pleural or pericardial effusion, as well as osteomyelitis, mastitis, abortion, disseminated infection, and cutaneous or soft tissue lesions such as abscesses. In one study, chronic weight loss was the most common sign in horses. Abortions seem to occur with or without respiratory signs, and some authors have suggested that they might be a form of localized disease. In one study, deaths were not reported in untreated mares with

coccidioidal abortions, and at least one mare later gave birth to healthy foals. Primary cutaneous infections might also occur in horses.

### *Ruminants and pigs*

Llamas seem to be particularly susceptible to coccidioidomycosis, and disseminated disease has been reported in this species. Overt illness has rarely been reported in cattle, sheep or pigs, but lesions suggestive of self-limited pulmonary infections can be seen in the lungs and thoracic lymph nodes at slaughter.

### *Other species*

Asymptomatic lesions or clinical signs can occur in a wide variety of other species. Fatal coccidioidomycosis has been reported in captive exotic animals including canids, felids, bats, wallabies, kangaroos, tapirs, Przewalski's horses and many species of nonhuman primates, as well as in wild cougars. Disseminated coccidioidomycosis was also documented in several southern sea otters (*Enhydra lutris nereis*) that were found moribund or dead in coastal waters of California, and in an emaciated, sick bottlenose dolphin in this region. In wild coyotes, lesions were reported as an incidental finding.

## Communicability

Coccidioidomycosis is not usually considered to be contagious; however, at least two cases of zoonotic transmission have been documented. In a recent report, a veterinary assistant developed a localized infection with osteomyelitis as the result of a bite from a cat with disseminated coccidioidomycosis. Another zoonotic case was apparently acquired by inhaling endospores, during the necropsy of a horse with disseminated infection.

## Post Mortem Lesions

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Gross lesions may be either disseminated or limited to the lungs, mediastinum and thoracic lymph nodes. The lungs are often involved, even in disseminated disease where the primary complaint is not respiratory. The lesions are characterized by foci of inflammation, which may be red to yellow, gray or white; miliary or nodular; and firm, caseous or liquefactive. Discrete nodules of variable size with a firm, grayish cut surface are often found. Mineralized foci may also be present. Effusions caused by C*occidioides* spp. are slightly cloudy, and are frequently tinged with red. If the heart is involved, the pericardium may be thickened and fibrotic, and it can be adhered to the epicardium. Affected lymph nodes are firm and swollen.

Varying placental lesions have been reported in horses that aborted. In one case, the placenta was thickened and leathery, with grayish white nodules. Similar nodules were also detected in the fetus. In another case, the placenta was edematous and congested but not leathery, and no nodules were found in it or in the lungs of the fetus.

## Diagnostic Tests

Establishing a diagnosis of coccidioidomycosis may be challenging in animals, and multiple tests including cytology, histopathology, culture and serology may be necessary. Adjunct tests such as radiographs can be helpful. Pulmonary lesions and hilar lymphadenopathy may be identified in small animals with respiratory disease, while animals with bone disease have lytic and proliferative lesions, with periosteal new bone formation. Advanced imaging studies may be useful in some cases. A trial with antifungal drugs is sometimes used to establish a presumptive diagnosis when other methods fail or are unacceptably invasive (e.g., a granuloma in the brain).

Coccidioidomycosis can be diagnosed by visualizing the parasites in tissues, exudates, transtracheal or bronchoalveolar lavage fluids, lymph nodes and pleural fluid. In the body, *Coccidioides* spp. form spherules, double-walled structures that vary widely in abundance and size. Most spherules are 20-80 µm in diameter, but some can be as large as 200 µm. They contain endospores, small, 2-5 µm globular structures that develop into new spherules when they are released. Spherules containing endospores are diagnostic, while spherules without endospores are presumptive evidence for coccidioidomycosis. In rare cases, the organisms may form hyphae in tissues or air spaces in the lung. The calcofluor white (CFW) fluorescent stain, potassium hydroxide (KOH) wet mounts, Grocott-methenamine silver stain, periodic acid-Schiff stain or hematoxylin-eosin stain can be used to visualize the organism. Organisms are occasionally found with Giemsa, Papanicolau or mucicarmine stains. Gram staining does not usually stain *Coccidioides* spp.

Coccidioidomycosis can also be diagnosed by culturing affected body fluids, exudates or tissue specimens. In-house fungal culture is not advisable, because the arthroconidia from mature cultures are readily aerosolized and inhaled. *C. immitis* and *C. posadasii* can grow on most fungal media such as Sabouraud agar, brain–heart infusion agar, potato dextrose or potato flakes agar, with or without cycloheximide, as well as on many media used to isolate bacteria. Because these organisms do not compete well with other fungi or bacteria, samples with mixed flora should be plated onto selective as well as nonselective media. Colonies can usually be detected within 4-5 days, but they can appear as late as 16 days. When they first appear, the colonies, which are often gray and membranous, can be difficult to recognize. Older colonies are usually floccose and variable in texture. They become white or buff, but can develop other colors as they age. The hyphae are hyaline and septate. Arthroconidia do not occur in young colonies, but develop as they age. They tend to be barrel-shaped and are approximately 2 to 4 µm in width, thick-walled and usually multinucleated. When combined with the presence of spherules containing endospores on direct microscopy, the presence of arthroconidia is diagnostic. Genetic probes to confirm the organism's identity are used routinely in

human laboratories, but veterinary laboratories will usually only report the presence of arthroconidia. *C. immitis* and *C. posadasii* are difficult to distinguish from each other; however, no differences between the clinical presentation and response to treatment are currently known, and identification to the species level is not routinely necessary.

Serology can be useful, but the techniques and their interpretation are not as well established in animals as humans. Agar gel immunodiffusion (AGID) assays for IgG and IgM are the most frequently used serological tests. ELISAs to detect IgM and IgG and the latex particle agglutination (LA) test for IgM are more sensitive than AGID, but can have false-positive results. In dogs and cats, positive results in these tests should be confirmed with AGID. In infected dogs, IgM can usually be detected within 2 to 5 weeks, and IgG develops approximately 8 to 12 weeks after infection. Unlike humans, the magnitude of the IgG titer does not seem to correlate with the severity of the disease in dogs, and titers in symptomatic and subclinically infected animals overlap. Some infected dogs can be seronegative or have low titers. According to some authors, serology is a weak diagnostic tool in cats; however, one study detected specific IgM in 82% of infected cats and specific IgG in 100%. Serological surveys of healthy and sick cats in endemic areas have not been published. Two studies in horses have been published recently. In a survey of clinically affected horses, titers tended to be higher in animals with more severe illness, but they overlapped between pulmonary and disseminated disease. Lower IgG titers were reported in horses with localized conditions such as coccidioidal abortion or soft tissue involvement without pulmonary signs. Another survey reported that few healthy horses in endemic areas are seropositive, and those animals tend to become seronegative with time. This suggests that even low titers may indicate active infections in horses if there are clinical signs.

## Morbidity and Mortality

*Coccidioides* spp. infections seem to be common among dogs in endemic areas. Approximately 70% of these infections are estimated to be subclinical. Infections are more common in young adult dogs and those that spend more time outdoors. In one prospective study, 27% of healthy 4- to 6-month-old seronegative puppies seroconverted during the following year, and approximately 5% developed clinical signs. In a second group of 4-18-month old dogs, 8% were seropositive and 3.4% had clinical signs. The cumulative probability of infection by 2 years of age was 28%, while the cumulative probability of illness was 6%. Another study reported that approximately 4% of the canine population in three endemic counties in Arizona becomes ill with coccidioidomycosis each year. Disseminated disease is estimated to occur in 20% of symptomatic dogs, but higher percentages have been reported in some studies. There are no long-term studies to determine whether recrudescence occurs in asymptomatically infected dogs.

Fewer cases of coccidioidomycosis have been reported in cats than dogs, and it is possible that they are more resistant to disease. However, clinical cases that are recognized in cats are often serious. Illness seems to be most common in middle-aged cats. In one study, there was no apparent link to feline leukemia virus or feline immunodeficiency virus infection.

Little is known about the prevalence of coccidioidomycosis in horses. A recent survey found that only 4% of healthy horses in endemic regions were seropositive. The titers in these horses decreased or disappeared over 2-6 months, and no horses in this study became ill. It is possible that many young or recently introduced horses are exposed and have a good immune response, but their titers become undetectable after a time.

Clinical cases are rarely seen in cattle, sheep or pigs, but asymptomatic infections may be common. Lesions have been reported in 5-15% of cattle slaughtered in some parts of Arizona, and in 2.5% of cattle slaughtered in Mexico. In some endemic regions of Mexico, 12% of the swine and 13% of the cattle were seropositive, and approximately 7% of cattle tested positive with the coccidioidin skin test.

The prognosis varies with the form of the disease and the treatment. Localized respiratory infections can be self-limiting and often have a good prognosis in dogs. One study reported that pulmonary disease with thoracic effusion, as well as disseminated disease, were fatal in approximately 90% of affected horses. Horses with pulmonary signs and no thoracic effusion were less severely affected, and two of six animals were treated successfully with antifungals. The survival rate was higher in horses with cutaneous lesions, mammary abscesses, or infections of soft tissues and no evidence of lung infection. No deaths were reported in untreated mares with coccidioidal abortion, and at least one animal later had healthy foals.

## Treatment

Dogs and cats with clinical coccidioidomycosis are usually treated with antifungal drugs. It is not known how many animals with primary respiratory disease would recover on their own, but significant numbers of dogs developed disseminated disease before oral antifungals became available. For this reason, treatment became common practice. There is some debate about this practice, since these drugs can have adverse effects and must often be given for months.

Antifungal drugs that have been used in dogs and cats include amphotericin B and azole drugs such as ketoconazole, itraconazole and fluconazole. There are a few reports of successful treatment of horses with conditions such as pulmonary coccidioidomycosis or vertebral osteomyelitis. Most animals are treated for at least 6-12 months. In disseminated disease, treatment is often continued for one to several years. Relapses can be seen.

## Prevention

Prevention is difficult in endemic areas, but it might be helpful to limit the animal's exposure to large concentrations of arthroconidia, such as those in desert soils, areas of soil disturbance and dusty conditions. Dust storms after a rainy season may contain especially high concentrations of aerosolized spores. No vaccine is available.

## Internet Resources

Centers for Disease Control and Prevention (CDC). Coccidioidomycosis.
http://www.cdc.gov/fungal/coccidioidomycosis/

eMedicine. Coccidioidomycosis
http://www.emedicine.com/EMERG/topic103.htm

Public Health Agency of Canada. Material Safety Data Sheets
http://www.phac-aspc.gc.ca/msds-ftss/index.html

The Merck Manual
http://www.merck.com/pubs/mmanual/

The Merck Veterinary Manual
http://www.merckvetmanual.com

## Acknowledgements

This factsheet was written by Anna Rovid Spickler, DVM, PhD, Veterinary Specialist from the Center for Food Security and Public Health. The U.S. Department of Agriculture Animal and Plant Health Inspection Service (USDA APHIS) provided funding for this factsheet through a series of cooperative agreements related to the development of resources for initial accreditation training.

The following format can be used to cite this factsheet. Spickler, Anna Rovid. 2010. Coccidioidomycosis. Retrieved from http://www.cfsph.iastate.edu/DiseaseInfo/factsheets.php.

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