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The Epidemiology of AIDS-Related Coccidioidomycosis in California

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The Epidemiology of AIDS-Related Coccidioidomycosis in California

by

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CHAPTER ONE: OVERVIEW OF COCCIDIOIDOMYCOSIS

Introduction

A. History

In 1894, Dr. Emmit Rixford reported the case of a protozoal infection before the San Francisco Medico-Chirurgical Society [1]. The patient was a farm laborer who had immigrated to the Central Valley of California to find work and had developed skin lesions from which the protozoan was isolated. Rixford recognized the organism as resembling that illustrated previously by Alejandro Posada in Argentina in 1892.

Rixford and his colleague, Gilchrist, convinced the organism was a protozoan, named it *Coccidioides* (meaning "coccidia-like" since it resembled protozoa) *immitis* (because they believed the disease was "not mild"). They also believed that the portal of entry was the skin. It wasn't until 1900 that Orphüls and Moffitt proved *C. immitis* was a fungus and five years later determined that the portal of entry was the lungs, elucidated its lifecycle and described its clinical spectrum [2]. By 1929, nearly 100 cases had been reported, and coccidioidomycosis was thought to be a severe, usually fatal disease.

At this time, the migration of farm workers into the Central Valley resulted in increasing reports of an acute, self-limited illness of unknown etiology. The illness is characterized by fever, cough, myalgia and pretibial erythema and is commonly known as "Valley Fever" or "San Joaquin Fever" [3]. Gifford and Dickson's studies in 1936 and 1937 linked coccidioidomycosis to Valley Fever and determined that disseminated coccidioidomycosis was a rare complication of the acute pulmonary infection [4].

Smith largely defined the epidemiology of coccidioidomycosis during World War II. He determined the incubation period of *C. immitis*, demonstrated the seasonal incidence of the disease and also developed diagnostic serological and skin tests still used today [5, 6].

B. Significance

Beginning in 1942 [7] numerous epidemics of coccidioidomycosis have been documented, but none have had the magnitude of the recent epidemic in California beginning in 1991. From the period of 1991 through 1993, the epidemic resulted in at least $60 million in direct health care costs [8]. As a result of the epidemic, and in an effort to better define the epidemiology of coccidioidomycosis, the Conference of State and Territorial Epidemiologists made coccidioidomycosis a regionally notifiable disease.

The first case of disseminated coccidioidomycosis in a person with the acquired immunodeficiency syndrome (AIDS) was reported in 1984 [9]. In 1987, the Centers for Disease Control and Prevention (CDC) made disseminated coccidioidomycosis (i.e., extrapulmonary) an AIDS-defining condition for persons infected with the human immunodeficiency virus (HIV) [10]. As the HIV epidemic moves inland from the coast in California, the number of cases of AIDS-defining coccidioidomycosis is likely to increase.

C. Outline

The rest of this chapter covers introductory material such as mycology, epidemiology and diagnosis. The next chapter focuses on the study of AIDS-defining coccidioidomycosis in California.

Mycology

A. Life cycle

Unlike most other fungal pathogens that infect humans no yeasts are present, and therefore no budding occurs. No other fungus comes close to producing the explosive numbers of progeny that *C. immitis* generates. *C. immitis* is the only arthroconidial fungus that produces a deep, systemic mycosis [11].

Reproduction of *C. immitis* is asexual and two morphologies are seen in its life cycle: the mycelial and spherule phases.

Mycelial Phase

C. immitis grows as a mold (the saprophytic form) in the soil during the mycelial phase. The mold grows in the form of branching, septate hyphae in which arthroconidia are formed as they matures. Arthroconidia are the infectious units of *C. immitis*. It usually takes at least 5 to 10 days for hyphae to mature. Once mature, the arthroconidia are very hardy and remain viable for long periods of time. Arthrospores are barrel-shaped and at maturity are 2 to 5 μm in length [12].

The hyphae are very friable and release arthroconidia with the slightest disturbance. The liberated arthroconidia are carried in the wind and can establish themselves in another soil site, continuing the saprophytic cycle, or alternatively infect an appropriate host. Infection of a human host is through inhalation of arthroconidia small enough to reach the lower airways. Cutaneous inoculation is rare, but it has been documented [13].

Spherule Phase

Within the terminal bronchioles the arthroconidia shed their outer hyphal cell wall, enlarge and become spherical. This characteristic tissue form, indicative of the spherule phase, has a thick cell wall and produces endospores, the reproductive units, as it matures. Spherules grow to up to 80 millimicrons in diameter [14].

Hundreds of endospores may be produced within a single spherule, and its rupture results in their release [11]. This is unique among the common mycoses. Therefore, a mature, endosporulating spherule is pathognomonic of coccidioidomycosis. Each endospore may produce another spherule, continuing the spherule phase, or be released from the body in contaminated fluids. If released into a saline soil environment, the endospores can revert to the mycelial phase and produce arthroconidia. Endospores, however, are not infectious, so person to person transmission is not possible except under very special circumstances. This can happen with formation of the mycelial phase on fomites at lower temperatures, such as on a plaster cast of a patient with an underlying coccidioidal skin lesion [15].

B. Laboratory Precautions

In the laboratory, handling of *C. immitis* cultures must be done with care since it is the mycelial phase that is growing in culture and infectious arthrospores are being produced. Numerous laboratory accidents have resulted in infections, some of which have provided valuable information regarding the lifecycle and pathophysiology of *C. immitis* [13, 16, 17].

Immunology and the Pathologic Basis of Disease in Coccidioidomycosis

The immunopathologic changes associated with coccidioidomycosis encompass a wide spectrum. In general, outcome of infection is related to the balance between an acute inflammatory reaction and a granulomatous reaction with development of adequate cell-mediated immunity [18]. If host resistance is adequate, granuloma formation is followed by fibrosis and scarring. If resistance is inadequate, as in rapidly progressive or disseminated cases, the acute inflammatory form predominates in a suppurative, destructive process. Several studies have shown *C. immitis* to induce production of proinflammatory cytokines from macrophages and monocytes [19-21]. Exaggerated production of these cytokines may lead to the clinical consequences of coccidioidomycosis [19].

Although both pulmonary and disseminated coccidioidomycosis lead to granuloma formation [4, 22], the suppurative process may be more marked in disseminated disease than in confined pulmonary infection.

A. The Importance of Cell-Mediated Immunity

In the initial infection of the previously unexposed host, cell-mediated immunity has not yet been established, and the immune system attempts to control the infection through an inflammatory process. In most cases the inflammatory response is able to control the infection until the individual develops cell-mediated immunity. This immune response is evidenced by a positive skin test to a coccidioidal antigen. Detectable cell-mediated immunity usually develops within two weeks of infection [3]. Data support the

notion that development of cell-mediated immunity is absolutely essential in the resolution of coccidioidomycosis and immunity to reinfection [23-27].

B. Antigenic Determinants of T Lymphocyte Stimulation

Stimulation of the T-cell line has been demonstrated with the proteins coccidioidin, derived from the mycelial phase, and spherulin, derived from the walls of spherules. Endospores also stimulate the T-cell line. Recently, a cell wall antigen (Ag2) of the mycelial and spherule phases of *C. immitis*, previously shown to stimulate T cells, was cloned in hopes of developing immunodiagnostic assays [28]. However, identification of the immunologic determinants of the host response to *C. immitis* is still needed.

In cases of deficient cell-mediated immunity, such as advanced HIV disease, the infection is progressive. It has been hypothesized that this immune defect is acquired and is specific for *C. immitis* since T-cell anergy is not exhibited to other organisms [29]. Anergy can result in negative skin tests but positive *in vitro* cellular immunity tests. The specific causes of T-cell anergy have yet to be determined [30], and much more work in this area is required for understanding of the molecular basis of disease severity. In patients with disseminated coccidioidomycosis, skin reactivity may wane as the disease progresses but may be reestablished upon recovery [12].

C. Specific Functions of T Lymphocytes

C. immitis is less likely to be totally destroyed in the host response than to be "walled-off" within a granuloma by T cells. Experiments on mice implicates the T_H-

helper cells of the subset one type (T_H1) as the important mediator of a successful immune response to coccidioidomycosis [31, 32].

Cytokines, elaborated by T lymphocytes, have an important role in inducing macrophagic resolution of infection. *In vitro* tests have shown the lack of production of interferon-gamma and interleukin-2 in subjects that are skin test negative [26]. Interferon-gamma, a product of T_H1 cells, leads to extensive accumulation and activation of macrophages against arthroconidia and endospores [33]. Interferon-gamma was shown to upregulate the protective immunity to *C. immitis* in mice whereas interleukin-4, a T_H2 cell product, down-regulates the protective immunity to *C. immitis* [31]. Interleukin-12 was shown to be protective against *C. immitis* in mice, by providing an early control mechanism that shifts production towards interferon-gamma.

D. Overview of Primary Infection

Cell-mediated immunity is paramount, and its interaction with other immune system participants takes place throughout the infectious process of *C. immitis*.

Immune Response to Arthroconidia

Only a single arthrospore is necessary for infection, but the likelihood of symptomatic illness and disseminated disease is related to the intensity of the exposure [34]. In the lower airways, arthroconidia evoke an early host response that consists primarily of macrophages [35] but also neutrophils attracted through complement-driven chemotactic factors [36]. Ampel and colleagues showed that macrophages have the capacity to destroy arthroconidia which is not dependent on prior host exposure to *C. immitis* [35].

Failure to Control Arthroconidia

Once phagocytosed by alveolar macrophages, some arthroconidia are able to resist being killed intracellularly by blocking fusion of the phagosome with the macrophage's lysosome [37]. T cell activation of macrophages is necessary to potentiate phagolysosomal fusion [23].

A portion of the hyphal outer cell wall remains attached to arthroconidia and is antiphagocytic to neutrophils and explains, in part, their ineffectiveness in this process [11].

Immune Response to Spherules

After surviving arthroconidia shed their hyphal cell walls, they enlarge to become spherules. For the most part, spherules generate a granulomatous, macrophagic response, but they are also attacked by neutrophils [38]. However, there is no evidence that spherules are killed by neutrophils.

The spherule has been the target of vaccine developers [39] and work continues on defining the spherule-derived antigens necessary for T-cell stimulation [40, 41].

Failure to Control Spherule Growth

Pathogenicity in coccidioidomycosis is largely due to spherule resistance to host cell defenses and the inflammatory response they initiate. The neutrophilic response to spherules is largely ineffective [42]. A component of the spherule wall itself interferes with the oxidative burst of neutrophils [34].

Immature spherules possess a dense, lamellated cell wall that presumably protects the spherule from the immune system during its enlargement [11]. The large size of more

mature spherules makes them resistant to phagocytic cells of the immune system [11], although giant cells may be able to phagocytose these larger structures.

Spherules are also capable of producing a protease which can digest opsonins, such as antibodies [43].

Immune Response to Endospore Release and Spherule Propagation

Upon spherule maturation and rupture, an acute inflammatory response again results with macrophages and neutrophils prominently involved. Endospores are released from spherules in packets held together by fibrillar material derived from the inner spherule wall. Multiple endospore packets are less easily phagocytosed than isolated endospores [44]. By the time the fibrillar material begins to disperse the endospores have already become small spherules. Neutrophils are attracted by endospores, but neutrophils can kill only 10%-20% of endospores [11] due to this clumping.

As in the case of arthroconidia, endospore survival of macrophage engulfment is a consequence of the failure of phagolysosome fusion in the macrophage [24, 45, 46]. Macrophage activation by T cells is necessary for efficient killing of endospores [24].

Involvement of Other Portions of the Immune System

1. Natural Killer Cells

Natural killer cells have a role in the control of spherules and endospores prior to the development of cell-mediated immunity [47]. Natural killer cells may therefore be able to eradicate early infections without development of T-cell immunity.

2. Eosinophils

There is an elevation of the percentage of eosinophils in the total white blood cell count during coccidioidal infection that may correlate with disease severity [48]. In a review of 17 patients with disseminated disease a CF titer of at least 1:32 or eosinophilia of at least 25% was 100% sensitive for determining if dissemination had occurred [48]. Since eosinophils cannot phagocytose spherules due to their size, the role of eosinophils in coccidioidomycosis is not known, although they may ingest immune complexes that are more prominent in disseminated disease [49].

3. Complement

Galgiani and colleagues have suggested that complement pathways activation by *C. immitis* may be defective in persons with disseminated disease [50]. Depression of specific components of complement, however, could not be clearly demonstrated in their study involving 23 patients.

4. Humoral Response

The humoral response to *C. immitis* infection results in the production of antibodies to coccidioidal antigens. Immunoglobulin M (IgM) is initially produced followed by immunoglobulin G (IgG) antibodies, but neither are protective. They do have diagnostic significance. Hyperproduction of IgE is notable in coccidioidomycosis because it correlates with disease severity. This is probably due to a decrease in the function of the T_H1 cell population that normally regulates IgE production [51].

Recently, Galgiani and colleagues reported detection of an antibody against a spherule wall protein that may be used in diagnosis of coccidioidal meningitis [52]

D. Infection in Immunocompromised Hosts

Conditions that disrupt T cell immune response integrity, such as HIV infection, thymectomy, corticosteroids, pregnancy or malignancies may result in increased susceptibility to symptomatic infection and virulence.

With cellular immunosuppression, macrophages cannot be maximally activated and are unable to halt advancement of the infection. Consequently these patients suffer progressive forms of coccidioidomycosis.

In a retrospective review of 77 HIV-infected patients with active, symptomatic coccidioidomycosis, the vast majority had CD4 counts less than 0.250×10^9/L [53]. In patients with AIDS, granulomas are poorly formed, less fibrosis occurs, and a greater number of spherules are found in comparison to patients without AIDS [54]. Reactivation of latent disease due to immunosuppression is also responsible for cases of coccidioidomycosis in HIV patients [55, 56], although the proportion of reactivated versus new infections is not clear.

E. Subsequent Infection

In a subsequent reinfection cell-mediated immunity has already been established, so arthroconidia or endospores can be efficiently destroyed by macrophages [46] or possibly neutrophils. Early activation of macrophages by T cells results in more efficient killing. Cytokines, such as interferon gamma [33], a product of T_H1 cells, lead to early, extensive macrophage accumulation and activation.

Clinical Syndromes

Coccidioidomycosis has a wide spectrum of clinical manifestations. The disease occurs in otherwise normal individuals but has an increased severity and predilection for immunocompromised people.

A. Primary Coccidioidomycosis

Following infection, the incubation period is usually 10 to 16 days [5]. If symptomatic, the patient usually undergoes a mild and self-limited disease over a period of three to six weeks and makes a complete recovery.

The distribution of primary coccidioidomycosis by clinical type was determined by Smith and colleagues during a landmark study of service personnel at four San Joaquin Valley Army Air Corps fields [5].

Asymptomatic

Nearly 60% of infections are asymptomatic or are indistinguishable from ordinary upper respiratory infections [5]. The only clues to past infection by *C. immitis* may be a positive skin test or chance detection of a coccidioidal cavity or nodule that has calcified on chest radiograph.

Symptomatic Pulmonary

Nearly 40% of infections are accompanied by pulmonary symptoms ranging from a mild influenza-like illness to frank pneumonia [5]. In symptomatic patients primary pulmonary lesions are most commonly parenchymal but can also be mediastinal or pleural [57].

Most of the cases that develop symptoms do so between one and three weeks following exposure [5]. A number of other systemic symptoms often accompany pulmonary manifestations. Werner's study [58] of acute coccidioidomycosis in archaeology students defined the most common symptoms as cough, fever and chest pain (usually pleuritic). These symptoms were present in 70% to 90% of all cases. Other common symptoms include chills, shortness of breath, malaise, myalgia, rash and night sweats. A headache is also very common and has the significance that the patient may be experiencing dissemination to the meninges, a dangerous occurrence. In another analysis of clinical features of primary coccidioidomycosis, similar symptoms were noted in students at the University of Arizona [59], and there was also a trend for symptoms to be more numerous in men than in women.

Consequences of Primary Pulmonary Coccidioidomycosis

About 5%-8% of episodes of primary coccidioidal pneumonia have pulmonary residua, generally nodules or cavities [34, 57] that can become calcified and radiodense.

Pulmonary nodules (coccidiomas) tend to develop in an area where pneumonia consolidates and becomes better defined in approximately 5 to 6 weeks [57]. Pulmonary nodules are generally sharply circumscribed, solitary, asymptomatic and tend to be located near the hila [60].

Pulmonary cavities are generally thin-walled, solitary and peripheral [63, 64]. The cavities tend to develop in granulomas and are usually asymptomatic and disappear within two years [57]. Cavities that are symptomatic may produce symptoms such as cough, chest pain in the cavity's region, hemoptysis, fever and night sweats [63, 64].

Due to the peripheral location of cavities, rupture into the pleural space is a possible, yet uncommon, occurrence [64].

Dermatological Aspects of Coccidioidomycosis in Primary Coccidioidomycosis

Toxic erythema is a nonspecific rash that that may accompany coccidioidal infection. When present, it generally occurs in the first few days of illness prior to the development of the hypersensitivity reaction and is characterized by a diffuse, erythematous rash that may cover the trunk and extremities. Often the rash will be gone by the time a patient seeks medical attention. Half of the archaeology students with coccidioidomycosis reported by Werner and colleagues [58] study displayed toxic erythema. The etiology of toxic erythema is unknown, and its presence seems to have no bearing on the outcome of coccidioidomycosis.

Valley fever is characterized principally by erythema nodosum and/or erythema multiforme and is often preceded by flu-like symptoms [3]. Although not specific to coccidioidomycosis, these erythemas are more strongly associated with the infection than is toxic erythema. Erythema nodosum is the most common of the erythemas to accompany primary coccidioidomycosis and tends to signify that dissemination will not occur; no therapy is warranted [12]. Erythema nodosum is characterized by painful, tender, hot, discrete and ill-defined nodules that usually occur on the shins. The appearance and associated pain tend to cause patients to seek medical attention [3]. This tends to occur about the same time as the skin test becomes positive and is considered to be a hypersensitivity reaction itself. Therefore, erythema nodosum is a convenient red flag that *C. immitis* infection has taken place. It is twice as common in women than in

men and uncommon in Blacks [3]. Erythema multiforme is also a hypersensitivity reaction to *C. immitis*. The urticarial-like papules associated with erythema multiforme can appear almost anywhere on the body, especially the trunk, extremities and the palms and soles. It is more common in children. Also included in the Valley fever complex are arthralgias ("desert rheumatism"), which generally involve the ankle, and a mild conjunctivitis [12].

B. Chronic Progressive Pulmonary Coccidioidomycosis

In approximately 5% of patients, the acute pneumonia does not resolve. Development of chronic progressive pulmonary coccidioidomycosis [57], in which greater and greater portions of the lung are involved, may occur with high risk of death [65]. Diabetic and immunocompromised patients are especially susceptible to chronic pulmonary coccidioidomycosis [30]. Nonwhites are also more likely to be patients with chronic progressive pneumonia [61]. Cavities often develop in the lungs of patients with chronic pulmonary coccidioidomycosis, and these may lead to empyemas or fistulae prolonging the chronic disease.

C. Diffuse (Miliary) Coccidioidomycosis

Diffuse pulmonary infiltrates may be seen in the early stages of hematogenous dissemination [66]. If the infiltrate persists in the lung, chronic progressive pulmonary coccidioidomycosis may develop [67].

D. Disseminated Coccidioidomycosis

Approximately 0.5% of infections with *C. immitis* result in destructive extrapulmonary lesions. The majority of cases, 73% in one study, of disseminated coccidioidomycosis originate as pulmonary infections [68].

Clinical Aspects of Disseminated Coccidioidomycosis

The most common sites for coccidioidal dissemination are skin, bones, joints and the meninges [34, 68]. *C. immitis*, however, is able to invade almost any organ or tissue. The meninges, soft tissue, synovium and bone are the most frequently involved [68].

The skin is the most common site of extra-thoracic spread [34]. Hematogenous dissemination results in cutaneous lesions, most commonly papules or verrucous lesions on the face [34].

Approximately one-third of patients with disseminated disease has bone or joint involvement. The skull, metacarpals, metatarsals, spine and tibia are the most commonly involved bones [68]. The ankle and knee are the most commonly involved joints [69]. In 90% of patients with joint involvement lesions are unifocal [65] which allows the successful therapeutic approach of injecting amphotericin B directly into joint spaces.

Spread to the meninges is a dangerous occurrence, and without therapy most patients will die within 12 months [70]. Treatment improves survival to greater than 50% [71]. Meningitis will generally occur within 6 months of the primary infection. Frequent symptoms are headache, nuchal rigidity, mental changes and diplopia [72]. Fever usually accompanies coccidioidal meningitis. The cerebrospinal fluid generally shows elevated leukocyte counts with the majority being mononuclear cells, although a large number of

these patients will have eosinophilia [73]. Early diagnosis and treatment correlate with successful outcome.

An analysis of 50 autopsies of patients who died from disseminated coccidioidomycosis showed genitourinary involvement to be common [74]. The kidney was the sixth most common organ to show evidence of disseminated coccidioidomycosis. Peritoneal, lymphatic and gastrointestinal involvement are rare [75, 76]. Dissemination may also lead to hepatic granulomas [77].

E. Primary Cutaneous Coccidioidomycosis

There have been cases of coccidioidomycosis in which infection was acquired not through the lungs, but through direct inoculation the mycelial form of *C. immitis* into the skin [78]. Primary cutaneous coccidioidomycosis, however, is rare.

F. Clinical Findings in Individuals Infected with HIV

In contrast to coccidioidomycosis in healthy individuals, a severe and often fatal disease occurs among patients with AIDS [79]. Fish and colleagues defined the clinical spectrum of coccidioidal disease during HIV infection in a retrospective review of 77 patients [53]. Pulmonary involvement, particularly diffuse pulmonary involvement, was the most common manifestation of coccidioidomycosis agreeing with a previous study [79]. Thirty percent of patients had clinically recognized disseminated disease to the meninges, lymph nodes, skin or liver, although dissemination could be demonstrated on autopsy in most cases [53, 79]. Many of the findings, such as skin involvement,

meningitis and focal pneumonia, in these patients are indistinguishable from those in otherwise normal hosts.

Coccidioidomycosis in HIV-infected individuals differs significantly from coccidioidomycosis in otherwise normal hosts. Patients may have hepatosplenomegaly, fever and rising coccidioidal antibody serum titers, a distinctive syndrome [80]. Bone and joint involvement is uncommon. Focal pulmonary disease presents with a cough and fever and may be mistaken for bacterial pneumonia [80]. Some patients will have no evidence of active disease with positive coccidioidal antibody tests, but 70% of these will go on to develop active disease [81]. As stated before, diffuse pulmonary involvement is common and this usually occurs at low CD4 counts (<200/μL) and also carries the highest mortality (70%) [53].

Diagnosis

The cornerstone of diagnosis is either culture recovery of *C. immitis* or its visualization in respiratory secretions or histopathological specimens. *C. immitis* cannot be definitively identified in its mycelial form. Spherules that have endospores must be identified to avoid confusion with other organisms [30]. Definite identification often requires conversion of *C. immitis* to the parasitic form by inoculation into animals or detection of antigens from *C. immitis* through culture [65].

Serologic tests are useful for diagnosis and prognosis. Skin tests have limited use in diagnosis. Specific DNA probes may eventually make current methods of diagnosis obsolete [82].

A. Skin Tests

Skin tests (dermal hypersensitivity) are commercially available. These can be used to detect current or previous infection by the fungus. Early disease may not be identified if T cell immunity has not yet developed. There are two preparations, coccidioidin and spherulin.

Coccidioidin, an isolate from the mycelial phase of *C. immitis* [83], was the first isolate from *C. immitis* to be used for dermal hypersentivity testing.

The use of coccidioidin in skin testing has largely been replaced by spherulin. Spherulin is an extract from the spherule phase of the fungus, the predominant form of *C. immitis* in humans, and has been used with adults since 1979.

Timing

If the exact time of arthrospore infection is known, coccidoidin reactivity is detectable by 10 to 12 days [3]. Patients with primary pulmonary coccidioidomycosis develop sensitivity to coccidioidin within 3 days to 3 weeks after the onset of illness, with more than 80% reactive during the first week of illness and 99% by the third week [83].

Specificity

Although cross-reactivity with antigens derived from *Histoplasma* and *Blastomyces* is rare [30], if coccidoidin is used in a concentrated form, such as a titer of 1:10, there may be significant cross-reaction with histoplamin [84]. One study found that exposure to *Histoplasma* did not affect reactivity to spherulin any more than coccidioidin [85].

Sensitivity

Neither skin test is able to identify all infections but spherulin is thought to be more sensitive than coccidioidin, particularly when identifying persons with chronic pulmonary cavitary disease, active pulmonary disease and disseminated disease. It has been shown to detect about one-third more cases of active coccidioidomycosis than coccidioidin in a study involving 53 patients [84]. Another comparison, however, found that coccidioidin was superior [85]. In cases of disseminated disease, spherulin is more likely to evoke a skin reaction than coccidioidin [12].

Anergy

Patients with a severe or chronic form of coccidioidomycosis typically have a negative skin test, and this limits the test's utility in diagnosis. In particular, Smith [83]

showed that 70% of patients with active disseminated disease did not respond to 1:100 dilution of coccidioidin. In addition, the majority of patients with severe disease who retained their skin test reactivity recovered, whereas the vast majority of those that did not retain reactivity died. If one survives disseminated disease, it is possible skin test reactivity will be reestablished [83].

The development of skin test anergy is a poor prognostic sign when coupled with prolonged or severe *C. immitis* infection [86]. Thus, anergy can be used as a marker for inadequate cell-mediated immunity.

The possible reasons for anergy include antigen overload, plasma factors that block cell-mediated immune reactions to *C. immitis* antigens and circulating immune complexes [30].

B. Visual Identification

A number of stains have been employed to identify *C. immitis* in specimens obtained from tissues, sputum or fluids. Some of the most common are KOH and Papanicolaou stains.

Specimens

C. immitis may be easily seen in pus [30]. In tissue specimens, a mature, endosporulating spherule of *C. immitis* is pathognomonic of infection and can be identified by the use of a variety of stains [65]. The surrounding tissue may show a granulomatous reaction. Immature spherules and endospores may be confused with host cells, artifacts and other fungi [34].

Bronchoalveolar lavage (BAL) specimens should be obtained when sputum samples are negative and the diagnosis of coccidioidomycosis is still considered.

Specimens obtained from fine needle aspiration of lung nodules should be examined for fungal organisms, taking care to distinguish the aspirate from carcinoma [87]. In cases of negative smears, culture may be required prior to initiating lung resection.

Visualization of the organism is rare in cerebrospinal fluid (CSF) [30, 88].

C. Culture

Isolation of the organism from a cultured clinical specimen is the definitive method of diagnosis [34]. *C. immitis* grows rapidly and readily on most media and can be detected as early as two days after inoculation of medium, although it may take up to one week. This is problematic in cases of rapidly progressive disease.

The mycelial phase is highly infectious and care must be taken in the laboratory to prevent accidental infection. The first of many recorded laboratory-associated infection with *C. immitis* came in 1929 when a medical student opened a petri dish of cultured *C. immitis* and inhaled arthrospores [4].

Specimens

Specimens for culture may be obtained from pus, sputum, fine needle aspirations, BAL fluid or biopsies.

Oher Fluids

Blood cultures are rarely positive [30], although fungemia due to *C. immitis* is a recognized manifestation of disseminated disease [89].

Cultures from urine, pleural effusions, gastric aspirates and peritoneal fluid are rarely positive [30]. CSF cultures are only positive about one-third of the time in patients with meningitis [30].

D. Serologic Tests

The humoral response to *C. immitis* is not protective, but detection of antibodies to coccidioidal antigens is useful to establish a diagnosis and to determine prognosis.

The serologic tests, tube precipitan (TP) and complement fixation (CF), used in diagnosing coccidioidomycosis are very specific [90].

The presence or absence of antibodies carries different meanings for the various manifestations of coccidioidal infection. Except for disseminated disease, negative serologies (both TP and CF negative) cannot exclude the possibility of a coccidioidal infection [90] soon after infection or in immunocompromised patients.

Tube Precipitan

The TP test identifies the presence of immunoglobulin M (IgM), indicating early infection [90]. In symptomatic infections, more than 50% of TP tests will be positive in the first week of illness. By the third week, the sensitivity of the test is better than 90%. The number of positive TP tests will begin to decrease following the third week to undetectable levels after five months.

Because of their lack of persistence, precipitins are not useful to diagnose disseminated disease, the later stages of primary infection or identification of coccidioidal pulmonary residua [90]. Precipitins do not have prognostic value.

Complement Fixation

The CF test identifies the presence of immunoglobulin G (IgG), which appears more slowly than do TP antibodies [90]. Therefore, both tests are necessary are necessary in order to maximize the number of diagnosed primary coccidioidal infections. Only one-tenth of CF tests are expected to be positive in the first week of illness. By the seventh month, nearly 90% of CF tests will be positive after an acute illness.

One of the most important uses of the CF test is to determine prognosis in a primary pulmonary infection. Smith and colleagues [90], found that a rising titer of CF antibodies indicates progressing infection. In their study, a titer of 1:16 to 1:32 indicated a greater possibility of dissemination. Also, a regressing titer is a favorable prognostic indication and has been used to follow response to therapy. The CF test remains the best method for the correlation of a patient's clinical status with a quantitative test [91].

CF antibodies in the cerebrospinal fluid occurs in 76% of patients with meningitis and have not been detected in patients without coccdioidal meningitis [90]. Therefore, the presence of CF antibodies is diagnostic of coccidioidal meningitis.

Immunodiffusion (ID)

Two immunodiffusion assays, IDTP and IDCF, mimic the TP and CF tests, respectively, and are commonly used in clinical laboratories due to the decreased amount of time necessary to identify specific coccidioidal isolates [92].

Latex Agglutination (LA)

The latex agglutination (LA) mimics the TP test but has been reported to be associated with frequent false-positive results [86, 91].

ELISA

In 1994, a newly released commercially available enzyme-linked immunosorbent assay (ELISA) was evaluated for its ability to detect IgM and IgG antibodies against the TP and CF antigens. In one study, the ELISA proved to be a reliable assay compared to the traditional approaches [93]. However, one of the problems with ELISA for identification of coccidioidal antigens is that antigen preparations are not pure. This results in considerable background activity [94]. An affinity-purified antigen was recently evaluated with enzyme immunoassay and showed 97% sensitivity and 100% specificity [95].

Other Antibodies

In coccidioidal meningitis, CSF cultures are often negative and CF antibodies may be undetectable in the CSF for a prolonged period of time. Antibodies against a 33-kDa spherule antigen were more commonly identified by ELISA than antibodies identified by the CF test [52]. Thus, anti-coccidioidal antibodies may be identified earlier resulting in quicker diagnosis in meningitis.

Eosinophilia

Eosiniophilia often accompanies acute symptomatic pulmonary infection. Eosinophilia in this situation may account for 5%-10% of the total white blood count

[12]. Marked eosinophilia of at least 20% has been associated with disseminated disease [96]. Eosinophilia may also be the only clue that disease has disseminated [48].

E. Diagnosis Difficulties Outside the Endemic Area

The greatest obstacle to diagnosing coccidioidomycosis is failure to consider it as a possibility, particularly in the non-endemic areas.

F. Diagnosis in People Infected With HIV

The diagnosis of coccidioidomycosis in HIV-infected individuals depends on a high degree of clinical suspicion, particularly in the non-endemic areas.

In more than 90% of all cases of clinical coccidioidomycosis in HIV-infected patients, the diagnosis is made with a positive culture, histologic identification of the fungus, or both [97]. Culture is a sensitive means of diagnosis, but may take up to a week to perform. In addition, examination of specimens by KOH or Papanicolaou stain are often negative [80]. For extrapulmonary disease, histological examination and culture of biopsy material is usually diagnostic.

Although serologic tests are often the first diagnostic tests performed, in fewer than 10% of cases, the diagnosis is solely based on serologic tests [97].
Fish and colleagues found that more than 70% of HIV-infected patients with active coccidioidomycosis will have positive serum for CF antibodies [98].

Unfortunately in very sick patients, serologic tests may fail. The classical CF and TP tests as well as the ID tests may be negative in patients with HIV [81, 98]. One study noted that 21% of HIV-infected patients with coccidioidomycosis had negative serologic

tests [99]. In particular, the diffuse, reticulonodular form of the disease in HIV-infected individuals is often associated with negative serologic tests [97, 98].

Serologic tests should be performed on all HIV-infected patients suspected of having coccidioidomycosis. In addition, coccidioidal infection in HIV-positive persons is associated with such high mortality that it is often recommended that HIV-infected individuals in endemic areas undergo periodic coccidioidal serologic testing. McNeil and Ampel [100] have recommended that testing for IgG antibodies should occur every six months in HIV-infected individuals living in endemic areas. Arguinchona and colleagues [81] identified patients with persistently positive serologic tests for coccidioidal antibodies (immunodiffusion test). They estimated that 70% of these patients will develop active disease over a period of 36 months.

Treatment

As regards therapy options, the overriding theme throughout the literature is that there have been few studies to compare therapeutic agents, optimal treatment regimens have yet to be defined and controversy surrounds choices and initiation of treatment. This area requires further research and characterization, especially given the prospects of a greater impact of coccidioidomycosis as an aggressive opportunistic infection in HIV-infected people.

A. General Principles

Most patients with mild, symptomatic primary coccidioidomycosis recover without therapy [34]. In particular, the presence of erythema nodosum or a positive skin test generally indicates that the infection will not disseminate and no therapy is required. Controversy surrounds decisions to treat moderate acute pulmonary coccidioidomycosis [34], although support for early treatment has been strengthened by a study based on cases reported to the Kern County Public Health Department [101]. This study showed a 78% decrease in the rate of dissemination and a 68% decrease in the rate of combined disease endpoints (dissemination, chronic disease and death) with early therapy. There is general agreement that severe primary infections warrant treatment, although data from controlled trials are lacking [65]. In patients with disseminated disease, prolonged chemotherapy is always indicated.

Individuals with symptomatic primary disease and within the high risk groups, such as those with elevated antibody (CF) titers, circumstances suggesting a high

innoculum of arthroconidia, increased susceptibility or a negative skin test are often treated aggressively due to increased risk of dissemination and severe disease [101].

Poor therapeutic outcome is often site-related, with infections of the bones, joints and meninges particularly difficult to manage [102].

B. Pharmacologic Therapies

Amphotericin B

Amphotericin B was introduced in 1957 and offered the first efficacious therapy for coccidioidomycosis. It is administered intravenously until resolution of infection. Symptoms such as nausea, fever and myalgias are common during administration [103]. Renal toxicity and shock are serious complications of amphotericin B use.

Due to its toxicity, particularly to the kidneys [103], therapy with amphotericin B is generally reserved for severe cases of coccidioidomycosis. Amphotericin B therapy is indicated in those patients with extensive and rapidly progressive pulmonary disease, with increased risk for dissemination or with documented disseminated disease [104]. Prior to the development of amphotericin B, coccidioidal meningitis was primarily fatal, although it remains the most serious form of disseminated coccidioidomycosis [104]. Intrathecal amphotericin B with the intravenous form is the standard since intravenous amphotericin B does not cross the blood-brain barrier in pharmacologic doses. Intrathecal therapy is generally required for one year with some physicians recommending lifelong intrathecal treatment [105]. Amphotericin B is also indicated for joint or pleural space involvement, and local injection can be a useful adjunct to systemic therapy.

Azoles

The emergence of the azoles as an alternative therapy for those patients who cannot tolerate amphotericin B has added a new dimension to the treatment of coccidioidomycosis [105]. These drugs have been used in an attempt to prevent disseminated disease, to treat limited disseminated disease and to provide follow-up therapy among patients whose conditions did not resolve with amphotericin B therapy [104]. Gastrointestinal side effects are common to the azoles, particularly among AIDS patients who may absorb oral drugs less easily.

These agents are attractive because they have less severe toxicity than amphotericin B and can be taken orally, although the overall response to treatment with azoles seems to be less than that of amphotericin B. In fact, almost one-third of cases on azole therapy relapse [104]. Properly controlled, randomized clinical trials have not yet been carried out for the azoles [86] but are in progress [65]. Although research is lacking in the area of treatment of primary disease with azoles, some physicians choose to treat moderate, primary infections with ketoconazole or, more likely, fluconazole [104].

As stated, relapse remains a problem common to all the azoles. In particular, coccidioidal meningitis presents a difficult challenge. Dewsnup and colleagues collected data on patients with coccidioidal meningitis who were treated with all of the oral azoles and found that 14 out 18 of these patients relapsed after completion of the therapy [106].

1. Miconazole

Miconazole was the first azole developed that showed promise as an anticoccidioidal agent [107]. Miconazole, however, showed high relapse rates [108]. It

is available only as an intravenous preparation. Its use is mainly as an alternative to amphotericin B in cases of local infection, such as joint or pleural spaces [65].

2. Ketoconazole

Ketoconazole was the first oral azole used against *C. immitis*. Its main side effects are gastrointestinal [109]. Although response to this agent is good, more severe manifestations of infection (progressive pulmonary and disseminated coccidioidomycosis) tend to relapse [110]. Ketoconazole may be used to treat moderate primary pulmonary infections [104].

3. Itraconazole

Itraconazole is a triazole, a newer class of azoles that has shown promise in treating primary coccidioidomycosis [111]. It has also shown efficacy in coccidioidal meningitis [112]. As with ketoconazole, gastrointestinal discomfort is the main side effect.

4. Fluconazole

This is a very important drug in the treatment of coccidioidomycosis. Fluconazole has fewer and less severe side effects than amphotericin B and is effective in the treatment of persistent infection and disseminated disease that calls for long-term therapy [113].

A study of the effectiveness of fluconazole in chronic pulmonary and nonmeningeal disseminated coccidioidomycosis showed it to be efficacious as a primary drug but also found a high relapse rate [114]. Fluconazole has also been studied as an alternative to amphotericin B for the treatment of coccidioidal meningitis and has been

shown to be effective in 79% of patients in an uncontrolled clinical trial over a 4-year period [113]. Although not as effective as amphotericin B for coccidioidal meningitis [104], it is an important alternative for patients who cannot tolerate or refuse intrathecal prolonged amphotericin B therapy.

Additionally, fluconazole is often used to treat moderate primary pulmonary infections [104]. Also, many recommend lifetime fluconazole therapy for HIV-positive patients after being treated for coccidioidomycosis.

5. SCH 51048

A new antifungal triazole, SCH 51048, has had superior results to fluconazole and itraconazole in an animal experiment [116] and may offer another treatment option soon.

C. Surgical Therapy

Patients may require surgery for cavitary disease or as a consequence of disease dissemination [117]. Coccidioidal cavities, if symptomatic, may need pulmonary resection. Surgery is indicated to drain empyemas and close persistent bronchopleural fistulae [65]. Granulomas involving bones (particularly the ribs) may require removal and the therapy of coccidioidal osteomyelitis is dependent upon surgery [104, 118]. Splenectomy may be required in cases of cavitation of the spleen.

Amphotericin B therapy is the most common chemotherapeutic adjuvant associated with surgical procedures.

D. Treating HIV-infected People

The optimal treatment of coccidioidomycosis in HIV-infected people is just starting to be established. Ampel and colleagues at the Tucson Veterans Affairs Medical

Center retrospectively analyzed 20 cases of coccidioidomycosis in HIV-infected people at their clinic since 1986 [119]. Twelve patients were treated with fluconazole, six were treated with amphotericin B and one each received itraconazole or ketoconazole. Several factors were significantly associated with treatment failure, including a diagnosis of AIDS, presentation with diffuse, reticulonodular pulmonary coccidioidomycosis, and initial treatment with amphotericin B. In particular, patients with diffuse, reticulonodular pulmonary coccidioidomycosis present the greatest difficulty since therapeutic failure is high (70% failure) and mortality is great [53, 55]. Oral azoles were successful in nearly 85% of cases and may be considered for initial therapy in focal pulmonary or disseminated disease.

For life-threatening coccidioidomycosis, especially the diffuse, reticulonodular pulmonary form, IV amphotericin B therapy is recommended as initial therapy [86].

Chronic maintenance treatment with azoles is needed in HIV-infected individuals to prevent relapse following initial treatment for coccidioidomycosis [53, 79, 105].

Epidemiology

The epidemiology of coccidioidomycosis in California was principally defined through the efforts of Smith and colleagues during World War II. Recently, the coccidioidomycosis epidemic in California has provided the impetus for renewed study and update of the epidemiology.

A. Endemic Area

The endemic area of coccidioidomycosis has been established by skin testing, proved cases and ecological studies at sites of epidemics [120]. Cases of coccidioidomycosis are usually sporadic, but there are occasional local epidemics among people involved in activities that disturb the soil in areas where *C. immitis* resides.

Geography

Coccidioidomycosis only occurs in the Western Hemisphere. Outside of the United States it occurs in Mexico and Central and South America [121] (Figure 1).

In the United States, the endemic area is in parts of six southwestern states: Arizona, California, Nevada, New Mexico, Texas and Utah [65]. The states with greatest endemicity for *C. immitis* are Arizona and California. Within the endemic areas the distribution of *C. immitis* is spotty. In California, the endemic area includes the entire Mojave and Sonoran deserts and extends up the Sacramento Valley to Red Bluff [122]. Kern County, the southernmost portion of the San Joaquin Valley, is the area of greatest endemicity for coccidioidomycosis in California and 25% of susceptibles may be infected per year [6].

Ecology

It has been noted that the area in which C. immitis is found coincides with that of the Lower Sonoran Life Zone [123].

There are many factors that lead to an area's ability to support the growth of *C. immitis*. The combination of rainfall, temperature, soil alkalinity and elevation lead to different degrees of endemicity of coccidioidomycosis. For example, although both Yuma, Arizona, and Florence, Arizona, have similar temperatures, more rainfall occurs in Florence making it one of the most endemic regions of coccidioidomycosis, whereas Yuma is only mildly endemic [123]. In general, the California portion of the Lower Sonoran Life Zone has the least rainfall of all the endemic areas. The low rainfall may make the soil too alkalinic to support abundant growth of the fungus and may explain why California has a lower incidence of disease compared to Arizona. However, the role of alkalinity of soils in which *C. immitis* lives is not clear [124].

1. Climate and Seasonality

C. immitis is distributed in an area characterized by arid and semi-arid climates, with hot summers and few winter freezes. It appears that *C. immitis* optimally grows when there is a definite period of very hot weather that has little or no rainfall. This apparently confers an advantage to *C. immitis* as drought destroys soil competitors [125].

When rain eventually falls the humidity in the surface soil provides a favorable climate for the bloom of *C. immitis* [123] and the consequent increase of arthroconidia. The extremes of both heavy winter rains and dry summers seem to be optimal for growth of *C. immitis*. Smith and colleagues [3] noted that more cases of coccidioidomycosis occurred in the hot, dry summer and fall seasons following rainy winters and springs than

in months following a lighter rainy season. The epidemic in California starting in 1991 was related to protracted drought followed by heavy rain [126].

Following the rainy season, the soil dries, and dust picked up by the wind carries away the arthrospores of *C. immitis*. Wetter winters inhibit the spread of dust, decreasing the number of reported cases, but also encourage the growth of *C. immitis* for the next season [5, 121].

The lowest temperature (in combination with other factors) that can support the growth of *C. immitis* in nature is 25°F and the most optimal temperature of growth for *C. immitis* is 35°C [123].

Coccidioidomycosis is described as a seasonal disease with case reports beginning to increase in late summer with most cases reported in the fall and winter months [34, 59, 124, 125].

2. Soil Conditions

C. immitis probably survives the summer heat in deeper soil, about 6 inches to 8 inches below the surface [127]. During the more mild climatic and soil conditions, *C. immitis* and its arthroconidia grow toward the surface. Soil that has been seeded and irrigated is much less likely to harbor *C. immitis* than that which has been uncultivated [11].

The role of changes in the soil pH and salinity are generally thought of as important for the growth of *C. immitis*, but these issues have not been investigated extensively [121].

B. Surveillance and Reporting

United States

Coccidioidomycosis is now a nationally notifiable disease for the southwestern states, and statewide data for California are now collected including age, sex, race, date of onset and occupation. The case definition developed by the CDC in collaboration with the Council of State and Territorial Epidemiologists includes laboratory criteria for diagnosis rather than just clinical suspicion. Unfortunately, information is not collected on the particular manifestation of coccidioidomycosis, such as disseminated disease, or if the patient was HIV-infected. In addition, risk factors are not reported case reports [8]. This information would be helpful in better defining the impact of coccidioidomycosis on particular populations.

Aside from the epidemic years, there is a higher rate of reported cases of coccidioidomycosis from Arizona than from California. It is not known whether this is due to over-reporting in Arizona, an under-reporting in California or a true higher rate of new cases in Arizona.

California

In a national meeting of experts held in Bakersfield in 1993, Kern County was singled out as exemplary in coccidioidomycosis surveillance since it links diagnostic testing to case reporting [126] ensuring the vast majority of cases are reported. This eliminates the dependence on providers to report cases. Kern County reports the majority of cases of coccidioidomycosis in California and, very likely, has the highest rates of coccidioidomycosis since it is situated in the most hyperendemic area of California.

Despite Kern County's efficiency, however, coccidioidomycosis is considered an underreported disease in California since other counties do not have this same infrastructure [17].

Prior to 1995, coccidioidomycosis was reportable in California, but only as weekly case counts by county. Hopefully the new case definition developed by the CDC and the increased awareness of coccidioidomycosis due to the epidemic years will lead to a more accurate reflection of the burden of coccidioidomycosis in California. In addition, the requirement that cases be confirmed by laboratory means sets up a possible link between reporting and diagnosis in the manner of Kern County's reporting system.

Coccidioidomycosis and AIDS Reporting

The AIDS Reporting System only collects data on AIDS-defining conditions. This means that only HIV-infected individuals who have not had a previous AIDS–defining illness or condition will be reported. In the case of coccidioidomycosis, only extrapulmonary disease is considered an AIDS-defining condition [10].

Disseminated coccidioidomycosis, for the purposes of the AIDS surveillance case definition, is: "*coccidioidomycosis at a site other than or in addition to the lungs or cervical or hilar lymph nodes with C. immitis identified by microscopy (histology or cytology), culture or detection of antigen in a specimen obtained directly from the tissues affected or a fluid from those tissues*" [10]. Therefore, diffuse pulmonary coccidioidomycosis and other conditions more common than disseminated disease in HIV-infected individuals [53] are not considered to be AIDS-defining opportunistic infections.

Subsequent opportunistic infections, including cases of disseminated coccidioidomycosis reported in patients previously defined as having AIDS, are not reliably reported. In combination with under-reporting, the number of cases of AIDS-related coccidioidomycosis underestimates the impact of coccidioidomycosis on the HIV-positive population.

C. Epidemics

Coccidioidomycosis is mostly associated with a background incidence of new cases from endemic areas during seasonal periods, but occasional outbreaks have served to help further define the endemic area [122] and to increase the awareness of coccidioidomycosis outside the endemic area.

Many of the endemic sites in California were defined because of wartime installation activities [128] or institutional field trips such as archaeological [58] or anthropological activities [129]. Epidemics are reported with greater frequency when related to activities that disturb the soil. The following are some important or illustrative outbreaks.

First Recorded Outbreak

The first documented California outbreak of coccidioidomycosis came in 1942 when seven graduate students on a field trip to retrieve biological specimens attempted to dig a rattle snake out of a squirrel hole in the Panoche Valley in San Benito County [7]. This first report was important in dispatching the long-held belief that coccidioidomycosis was always a deadly disease.

Outbreaks of Coccidioidomycosis and the Military

Military activities in California have provided the opportunity to study coccidioidal infection in persons not previously associated with the area and helped define the endemic area. The first of many epidemics reported in association with military training maneuvers and facilities was recorded in the literature in 1944 [130]. The military's understanding of the risks of activities in the coccidioidal endemic area is largely due to the work of Smith [3, 6].

San Diego 1961

There are documented cases of importing *C. immitis* into non-coccidioidal areas causing an outbreak of coccidioidomycosis. An outbreak in a residential area of San Diego County was reported in 1961 and was due to topsoil that was brought in from an old Indian campground. Twenty-four cases resulted over a period of several years [131]. This occurrence was particularly interesting since *C. immitis* was able to establish itself for a long period of time. This same patch of soil provided isolates of *C. immitis* for more than a ten-year period.

Dust Storms

An extraordinary feature of coccidioidomycosis is that the arthroconidia can be spread hundreds of miles to areas of susceptible hosts in dust storms. A large dust storm in Kern County in December of 1977, resulted in more than 500 new cases of coccidioidomycosis, most of them (359) from non-endemic areas of Northern California, such as San Francisco [132]. Fortunately, rains in the non-endemic and endemic areas

soon ended the epidemic, but the impact of such an occurrence may likely be underestimated since cases outside of the endemic area are less likely to be recognized.

California 1991-1994

Between 1981 and 1990, the average number of cases of coccidioidomycosis reported in California was 428 [8]. The number of new cases increased from 441 in 1990 to 4,516 in 1992 [Stanley Bissell, personal communication]. Cases began to decrease in 1993 with 4,130 and are beginning to approach pre-epidemic levels (956 cases reported in 1996). In the years of 1991 through 1994, more than 12,500 cases were reported with Kern County accounting for 67% of those reported (Figure 2). In 1991 it was estimated that 1.1% of the total population of Kern County (then almost 550,000 people) became infected with *C. immitis* with almost all of the cases occurring in the last four months of the year when the epidemic began [125].

The reasons for this epidemic may be related to rainfall patterns, immigration of new, susceptible groups, increased land development in endemic areas, and perhaps improved diagnosis and reporting due to publicity around coccidioidomycosis [126]. This epidemic was unique in that it lasted for four years and spread over a significant portion of the state.

Northridge Earthquake, January 17, 1994

An earthquake in Northridge, California resulted in 170 cases of coccidioidomycosis from Ventura County, a county not normally known as highly endemic for coccidioidomycosis [133]. Dust clouds emanated from landslides in the Santa Susana Mountains and easterly winds carried the dust into the Simi Valley.

Residents of the Simi Valley comprised 56% of the cases of coccidioidomycosis in Ventura County even though the Simi Valley accounts for only 15% of the population of the county [134]. The attack rate in Ventura County was 30 cases per 100,000 population, and in Simi Valley, the attack rate was 114 per 100,000 [134].

D. Prevalence of Skin Test Reactivity

Skin testing reflects the extent of endemicity of coccidioidomycosis is an area. Large-scale skin testing has only taken place in the endemic areas of California and Arizona. Between 50% and 80% of people living in endemic areas have a positive skin test indicating prior exposure to *C. immitis* [104].

Outside California

The prevalence of dermal hypersensitivity to coccidioidal antigens in long-time residents of Tucson was found to be 57% [85].

California

In Kern County, skin testing has been carried out on a widespread basis for more than 60 years [135]. The overall percentage of high school and elementary school students showing a positive skin test had been decreasing over time until the recent epidemic. In the periods of 1937 to 1939, 1959 and 1964 to 1965 the percentage of high school students having a positive skin test was 68%, 40% and 22%, respectively. For elementary school students in the same time periods the figures were: 55%, 17% and 6%.

In 1984, the percentage of eighth graders with positive skin reactivity to spherulin was 7% [125]. For first graders it was 2.8%. Performed again in 1992, during the peak of the epidemic, the overall skin reactivity amongst eighth graders was 13.6% and

amongst first graders it was 6.7%. The rarity of persons with skin test reactivity in 1984 may have reflected a population with growing susceptibility to coccidioidal infection contributing to the dramatic increase in cases during the epidemic years.

E. Incidence

There are approximately 100,000 new infections by *C. immitis* every year in the United States [121]. Almost all of these infections occur in the six southwestern states that encompass the endemic area. A much broader impact of this previously regional disease is now appreciated since cases are increasingly recognized outside the endemic area. These cases may be due to travel to an endemic area, reactivation of a previous infection or through fomite transfer. The mobility of certain groups, such as the military, brings the disease out of its usual environment and makes diagnosing it challenging for physicians unfamiliar with coccidioidomycosis [136].

The incidence of infection is likely to increase in the coming years because of population growth in the endemic areas [126]. In particular, the incidence is likely to increase within the HIV-infected population; a prospective study within an endemic area of Arizona indicates that 10% of HIV-positive patients will develop active coccidioidomycosis per year [55].

Outside California

1. General

During the period of 1990 through 1995, the number of reported cases in Arizona increased 144% [137]. During the period of 1980 through 1989, the median annual number of reported cases of coccidioidomycosis in Arizona was 211. The annual number

of cases reported increased from 255 (7.0 cases per 100,000 population) in 1990 to 623 (14.9 cases per 100,000 population in 1995). The reasons for this increasing incidence in Arizona are not clear.

2. People Infected with HIV

A prospective study demonstrated a cumulative incidence of active coccidioidomycosis among HIV-infected people living in Tucson, Arizona of nearly 25% after 41 months of follow-up [55]. For this particular area, this is nearly 20 times the rate of active coccidioidomycosis for a population of university students living in the same area [59].

Ampel and colleagues defined the risk for an HIV-positive person, in the endemic state of Arizona, of developing active coccidioidomycosis as 6.5% [55]. In Tucson, Arizona, coccidioidomycosis is the third most common opportunistic infection associated with HIV-infected people [55, 79].

California

Prior to the epidemic starting in 1991, the infection rate (the percentage of those becoming coccidioidin positive per year spent in the Kern County area) among high school students dropped in a similar manner as the decrease in the prevalence of skin test positivity over the same period. For the periods of 1937 to 1939, 1959 and 1964 to 1965 the rates of infection were 10%, 4% and less than 2%, respectively [135].

Between 1981 and 1990 the average number of reported cases of coccidioidomycosis in California averaged 428 per year [8]. From 1991 through 1994, 12,549 cases of coccidioidomycosis were reported to the California Department of Health

Services (personal communication, Stanley Bissell, California Department of Health Services, Sacramento, California). Incident cases peaked in 1992 with 4,516 and have decreased steadily to 956 in 1996.

The populations of two counties in the southern San Joaquin Valley, Kern and Tulare, are much more affected by *C. immitis* than other counties of California. From 1987 through 1990, Kern reported 1,030 cases of coccidioidomycosis whereas Tulare reported 90 during the same time period (personal communication, Stanley Bissell, California Department of Health Services, Sacramento, California). Kern County has reported 63% of all cases of coccidioidomycosis in California for the last ten years and Tulare county has reported 8%.

From 1940-1990 the average number of cases in Kern County was 37/100,000/year [125]. For Kern County, 1990, 1991 and 1992 case rates were 51, 211, 572 per 100,000 population, respectively. For neighboring Tulare County, the case rates were 26, 53 and 171 per 100,000 population for the same time period [124, 138]. The population in both of these counties grew 3%-4% during that period, and the arrival of these new susceptibles may have contributed to increase of case reports [124].

F. Factors Influencing Infection Rates

Risk Factors for Infection

C. immitis infects persons of any age, gender or racial or ethnic group [104].

Risk Groups for Symptomatic Cases

Erythema nodosum, the hypersensitivity reaction to coccidioidal infection, is far more common in women than in men and uncommon in Blacks [3]. It has also been observed that coccidioidomycosis is more severe in very young and very old people [104]. Additionally, the role of diabetes mellitus as a risk factor for incident coccidioidomycosis and residual pulmonary sequellae is controversial [139]. Historically, symptomatic pulmonary disease has been reported as having a slight male preponderance but no racial or ethnic predilection [104]. Recent epidemiological studies in Arizona and California due to the epidemic and increased reporting requirements in the endemic areas have begun to better define these groups.

1. General

A recent analysis of cases reported to the Arizona Department of Health Services confirmed that most of the reported cases (symptomatic) of coccidioidomycosis occurred in males (63%) [137]. Since 1995, California has been collecting data on cases of coccidioidomycosis by race and gender. For 1995 and 1996, males were reported as 60%, 62%, 63% and 79% of cases of Whites, Asians, Hispanics and Blacks, respectively (personal communication, Stanley Bissell, California Department of Health Services, Sacramento, California).

At the beginning of the California epidemic, a retrospective study analyzed demographic data associated with cases in Kern County [125]. Whites made up only 43.0% of infections but 62.7% of the population of Kern County. Hispanics comprised 35.5% of patients but only 27.7% of the population of Kern County. Filipinos comprised 7.7% of infections but only 1.5% of the population of Kern County. African-Americans

comprised 6.7% of infections compared to 5.5% of the population of Kern County. Twenty-six percent of the cases of serious disease occurred in African-Americans. In addition, eight percent of the patients were diabetics, and 22% of serious cases of coccidioidomycosis were in diabetic patients.

The risk factors for acquiring coccidioidomycosis are exposure to dust during dry and windy conditions or because of exposure to soil. Occupational soil exposure (such as archaeology or construction work), in particular, has long been thought of as important in acquiring coccidioidomycosis [140]. However, the same retrospective study previously mentioned found no role of occupation associated with cases at the beginning of the California epidemic [125]. In a case-control study to identify risk factors for acquiring acute coccidioidomycosis following the Northridge earthquake, researchers found that physically being in a dust cloud and the amount of time spent in a dust cloud significantly increased the risk for being diagnosed with acute coccidioidomycosis [134]. This supports the long-held notion that the risk of symptomatic infection increases with greater innoculum.

Age is a risk factor for symptomatic coccidioidomycosis. A recent study reported that the attack rate was 2.8 times greater for those 40 years or older than for those younger than 40 years old [134].

2. Immunocompromised Hosts

A $CD4^+$ lymphocyte count of less than 0.250×10^9/L has been shown to be significantly associated with the development of active coccidioidomycosis in HIV-infected individuals [55]. A diagnosis of AIDS and anergy on dermal hypersensitivity testing were also associated with development of active coccidioidomycosis. The

proportion of new cases versus reactivated cases in this population is not known. National vital statistics have further demonstrated the emerging association between coccidioidomycosis and HIV infection [141]. From 1987 to 1992, the percentage of people with coccidioidomycosis listed on their death certificate that were also infected with HIV rose from 13% to 32% [141].

Symptomatic coccidioidomycosis is frequently found in persons with other forms of immunosuppression such as transplants, steroid use and malignancies [66, 142, 143].

Pregnancy has long been thought of as a risk factor for serious coccidioidomycosis [143], but this too is being reconsidered, since more recent studies have been inconclusive or have shown coccidioidomycosis is a rare complication of pregnancy even in an endemic area [144, 145]. Pregnancy is discussed further in association with disseminated disease.

Risk Groups for Disseminated Disease

Disseminated disease afflicts a small minority of patients with certain racial, age and other groups having increased risk for dissemination. Dissemination can occur with or without symptomatic pulmonary involvement. Approximately 0.5% of *all infections* (symptomatic or asymptomatic) by *C. immitis* disseminate beyond the lungs [5]. Pappagianis has reported rates of dissemination among *clinically diagnosed* cases of coccidioidomycosis as 4.2% [132] and 5.7% [121, 124].

1. Gender

In the analysis of cases at the beginning of California epidemic, 76% of cases of disseminated disease were males [125] reaffirming the preponderance of disseminated

disease among males that has been known since coccidioidomycosis was a recognized disease [5]

At least one study has questioned this increased rate in males. Drutz and Huppert [11] stated, "Men may spend more time in agricultural or outdoor activities giving greater innoculum. But under appropriate conditions women may be just as susceptible."

2. Age

The frequency of dissemination and the risk of fatal outcome were shown to be increased if the patient is five years of age or younger or 50 years of age or older [146].

3. Racial/Ethnic

Many racial or ethnic groups have been associated with an increased risk of disseminated disease compared to Whites. There is solid evidence that Blacks and Filipinos are at increased risk for disseminated disease. It is likely that Native Americans are at increased risk. Various articles have reported that all *non-whites* are at increased risk [120], resulting in Hispanics and Asians being lumped into the group of those considered to be at increased risk for disease dissemination. More studies need to be performed in order to sort this out.

Whites are less likely to have disseminated disease compared to other racial or ethnic groups. Smith and colleagues' study of the proportion of the different clinical aspects of coccidioidomycosis was based largely on a study of young white males [5]. Among clinical cases, approximately a 1% rate of dissemination occurred. During the first three months of the California epidemic, Whites had a dissemination rate of 2.2% of seropositive cases [138].

Pappagianis [121] has reported a rate of dissemination for Filipinos of 21% of cases. During the first three months of the California epidemic, Filipinos had a dissemination rate of 7.3% of cases [138]. The authors of the latter study hypothesized the difference between these two findings may be that the previous study took place before the advent of aggressive drug therapy in this population.

Smith [5] determined that Blacks had a rate of dissemination that was ten times more frequent than the rate for whites. Similarly, during the first three months of the California epidemic, Blacks showed dissemination of 22% of reported cases [138] which was a proportion 10 times that of Whites.

Hispanics have been reported in the literature to have an increased risk of disseminated disease [12, 104], but this is questionable. During the first three months of the California epidemic, Hispanics had a dissemination rate of 3.4% of cases, an amount similar to that of Whites [138].

Sievers [146] showed that Native American Indians were three times more likely than Whites to develop disseminated disease and five times more likely to die from it.

It has been suggested that Asians are at greater risk for dissemination compared to Whites [104]. Case reports, unfortunately often deal with small numbers of patients that are of Asian background. Following the dust storm in 1977 in Kern County, it was reported that 35% of cases of coccidioidomycosis in Asians disseminated [147]. During the first three months of the California epidemic, Asians had a dissemination rate of 20% of cases [138]. (There were only ten total cases.)

4. Disseminated Coccidioidomycosis and HIV Infection

The frequency of extra-pulmonary manifestations of coccidioidomycosis seems to be much higher in HIV-infected individuals than in immunocompetent hosts. At least 25% of patients identified for a retrospective review of HIV infection and concomitant coccidioidomycosis had disseminated disease [53].

During the six-year study period of 1987 through 1992, the risk of an HIV-positive person having disseminated coccidioidomycosis as an AIDS-defining illness was 0.27% for the United States [141]. The racial predilection for disseminated coccidioidomycosis was not supported by the data in this study leading the authors to conclude that once immunosuppressed by HIV, non-Black persons are just as susceptible to dissemination as Black persons. Of note is that 63% of the patients with disseminated coccidioidomycosis died within one year of the AIDS diagnosis. This high mortality rate is comparable to other reports [79].

In a retrospective analysis of 91 cases of coccidioidomycosis in HIV-infected individuals at a medical center in Arizona, coccidioidomycosis was the AIDS-defining illness in 37 (41%) [99].

5. Other Immunocompromised Hosts

Immunosuppressed patients may have disease dissemination due to a new infection or reactivation of a latent infection. The proportion of new versus reactivated cases is not known.

In endemic areas, disseminated coccidioidomycosis has been reported as a significant cause of maternal mortality with mortality rates at least 20% [143]. In a retrospective analysis from 1950 through 1967, coccidioidomycosis was found to be as common a cause of maternal mortality in the southern San Joaquin Valley as any other

cause [148]. It has been suggested that patients who develop coccidioidomycosis during pregnancy should undergo regular serologic studies in anticipation of possible dissemination [149].

The dissemination rate during pregnancy has been reported to be 40 to 100 times that of the general population and is higher in non-White races [143]. Drutz and Huppert hypothesized that immunosuppression in pregnancy is not severe enough to account for the virulent course of coccidioidomycosis that is encountered since pregnancy seems to pose no increased risk for a woman with a past history of arrested coccidioidomycosis [11]. Suppressed cell-mediated immunity and increased hormone levels may act in combination to increase the risk of dissemination in pregnant women (which have been shown to stimulate fungal growth since they have sex hormone receptors) [11].

The later coccidioidomycosis is acquired in pregnancy, the more likely it will disseminate [150]. Dissemination during the later stages of pregnancy has been associated with fetal death.

Any condition associated with immunosuppression such as organ transplantation, immunosuppressive therapy (steroids, chemotherapy) or malignancies may increase the risk for reactivation of latent infection and dissemination or new infections [34, 104, 151].

G. Fomite Transmission

Infection by *C. immitis* by fomite transmission has been extensively documented. An employee of a cotton processing plant in Georgia developed coccidioidomycosis after unloading cotton from the San Joaquin Valley [152]. A mechanic in Oregon, who had

never traveled to an endemic area, worked on trucks that had passed through the Central Valley of California and developed disseminated coccidioidomycosis [153].

Prevention & Control of Coccidioidomycosis

A. General

Coccidioidomycosis is a serious disease in terms of morbidity and mortality. It contributes to increasing health care costs and can potentially affect the economy of endemic regions. As noted previously, the epidemic of 1991 through 1993 resulted in $60 million in direct medical services. This did not include indirect costs associated with lost wages and a decrease in tourism due to reluctance of travelers to visit the Central Valley.

Exposure

During World War II Smith focused on dust control at military bases in order to prevent infection among susceptible personnel in endemic areas [5]. Much of our understanding of the effectiveness of such measures on coccidioidal infection came from this work. Activities such as limiting construction during months of peak infection rates, planting lawns and paving roads resulted in a one half to two third decrease in the attack rates among susceptible persons. Despite such efforts, the disease remains an occupational hazard for military personnel in the endemic area [154].

Attempts to control *C. immitis* would prove difficult, as it is a natural and persistent inhabitant of the environment. Fungicides only work to a certain depth and cannot possibly cover the extensive area of the endemic region [8]. The ubiquitousness of *C. immitis* in its natural environment makes other measures, such as the use of respirators for construction workers, impractical for long term exposure control for residents of the endemic area. In addition, winds can carry easily airborne arthrospores to areas previously thought to be free of *C. immitis* [140].

Recommendations for short-term exposure prevention has focused on particular, susceptible groups, such as students engaging in soil-disturbing field work in endemic areas or military personnel. There are published guidelines for employers of workers in soil-related activities in the endemic area [140]. Susceptible persons can be identified with skin testing and non-reactors should be advised of the implications of the test. Local dust control measures in areas of investigation for archaeologists and others performing fieldwork are feasible on a small scale. Local prevention measures may entail wetting the ground, sleeping upwind of digging sites and using masks while working.

Vaccine Development

Due to the nature of infection by *C. immitis* and normal immunity to exogenous reinfection it was proposed that a vaccine would be appropriate for preventing coccidioidomycosis. The Valley Fever Vaccine Study Group, however, did not find a vaccine of killed spherules to be protective in a study involving nearly 3000 human subjects from 1980 to 1985 [39]. This is particularly unfortunate given the high mortality of coccidioidomycosis in HIV-positive people [53]. Therefore, the whole organism is not the ideal vaccine candidate. Vaccination of individuals with selective antigens is ideal, but these antigens have been difficult to identify [151]

With further advancements in our understanding of the biological basis for immunity to *C. immitis* and the general advancement in techniques of molecular biology, coccidioidomycosis still seems to be a logical target for vaccine development. Current studies are examining the use of purified antigens for vaccines [65]. Unfortunately, it is unlikely the development of a vaccine would not be embraced manufacturers due to the limited commercial market. This is evidenced by the intermittent nature of vaccine

research for the past 30 years [8]. However, coccidioidomycosis has long been and continues to be a preventative medicine problem for the armed forces as large numbers of service personnel are still deployed in the endemic areas [155]. This problem is complicated by infections that may manifest themselves after personnel have left the endemic area [156], which presents a greater challenge to maintaining the health of service personnel. This may be the right time for a new public-private partnership to be forged among commercial biotechnology firms, the Department of Defense and the Public Health Service to develop a vaccine that would be mutually beneficial to the interests of all [155].

B. HIV-infected Population

Prevention of coccidioidomycosis is extremely important in this population since clinical manifestations are severe and mortality is high [55, 79].

Exposure

As noted previously the intensity of exposure is associated with the severity of infection. Therefore, HIV-positive persons living or visiting endemic areas may want to avoid activities or occupations that increase their exposure to dust and soil such as performing agricultural or construction work [86]. Although some experts have recommended that persons with AIDS avoid endemic areas during late summer and fall [157], there seems to be no evidence to suggest that HIV-positive persons should be discouraged from living or visiting endemic areas [86].

Patients with HIV are at increased risk for all sorts of pathogens wherever they live or travel and should be made aware of the effects of the pathogens of the local environment in order to make decisions about residency and travel [119].

Prophylaxis

Studies using fluconazole as a daily prophylaxis to prevent coccidioidomycosis in AIDS patients living in endemic areas are in progress [119, 157]. Experts are waiting for these results before calling for prophylactic treatment against coccidioidomycosis for HIV-positive patients in endemic areas.

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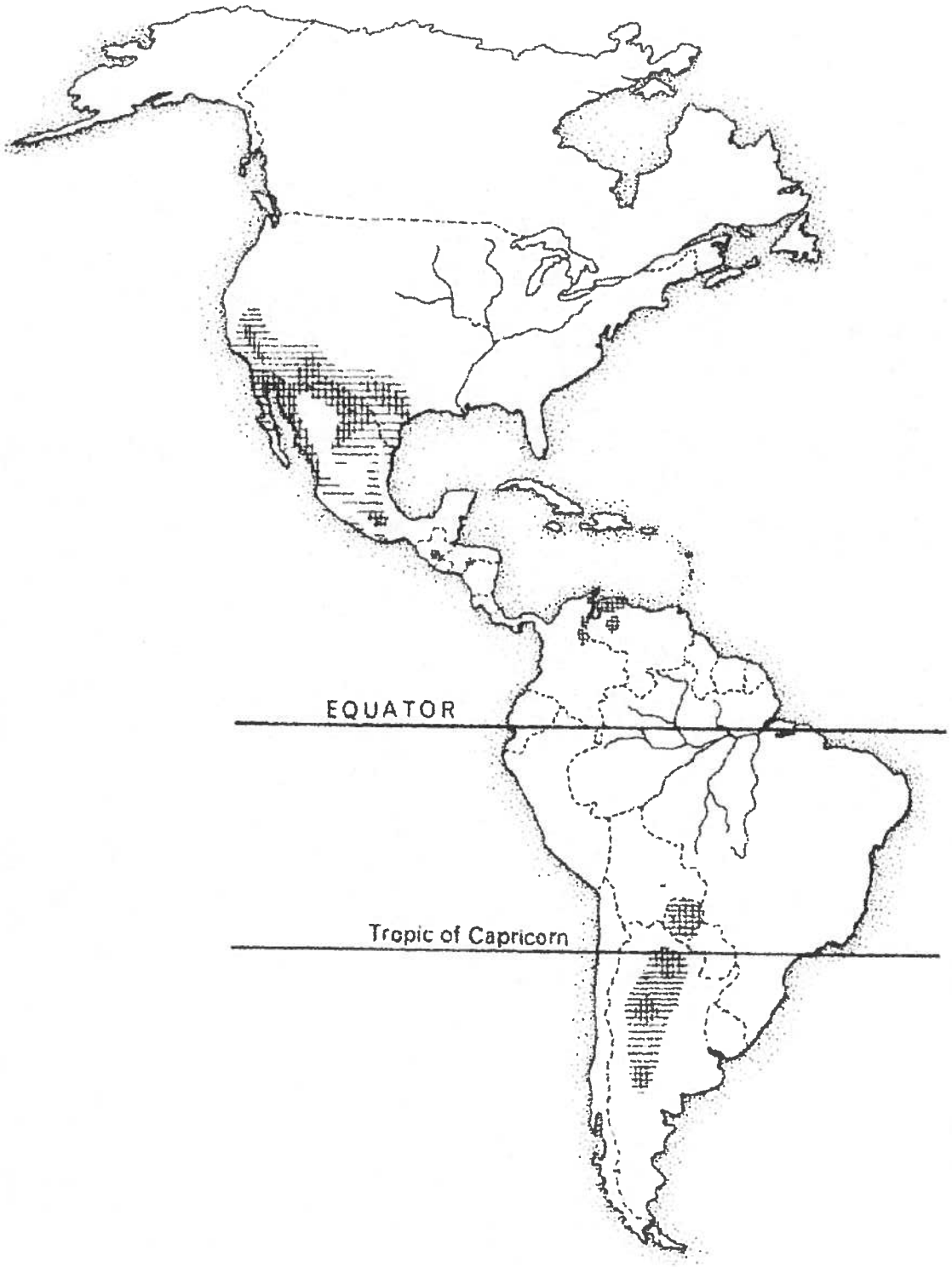

Figure 1: Endemic Areas of Coccidioidomycosis (shaded).

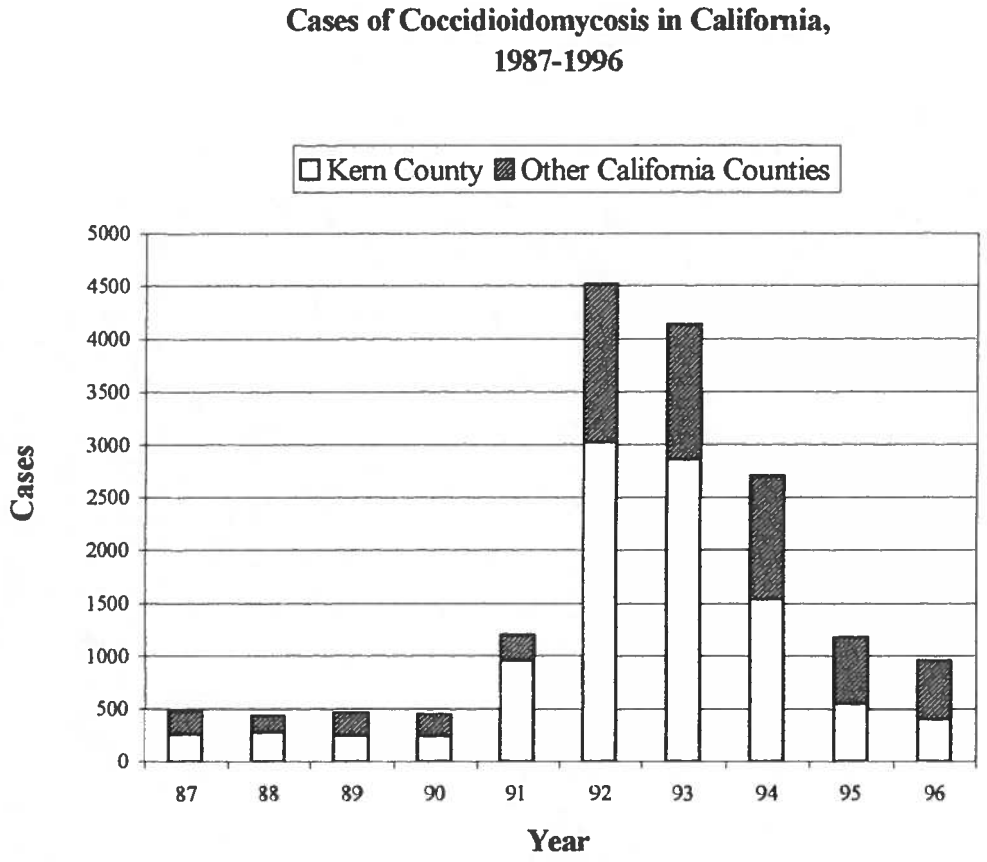

Figure 2: Cases of Coccidioidomycosis in California, 1987 – 1996.

CHAPTER TWO: AIDS-RELATED COCCIDIOIDOMYCOSIS IN CALIFORNIA

Introduction

A. Significance

Disseminated coccidioidomycosis became an AIDS-defining illness in 1987 [1]. Although coccidioidomycosis is a relative latecomer to the group of opportunistic infections in individuals infected with HIV, it has been described as an emerging disease. This may be because the HIV epidemic is moving from urban to rural areas that may be more likely to be endemic for coccidioidomycosis. Also, people infected with HIV may be living longer with common opportunistic infections due to more experience with treatment and prophylaxis. Therefore, coccidioidomycosis may be likely to be more common as an opportunistic infection as the HIV epidemic continues.

The epidemic of coccidioidomycosis in California was unique in its impact and scope and may have had a profound effect on the HIV-infected population. It is not known, however, if coccidioidomycosis among HIV-infected patients is primarily due to new infections, as would likely occur during an epidemic, or due to reactivation of latent infections.

In endemic areas of Arizona, the clinical and epidemiological aspects of coccidioidomycosis and HIV have been studied with increasing intensity over the past ten years. In these studies, coccidioidomycosis has been shown to be a significant cause of morbidity and mortality. Tucson, Arizona, like Kern County, California, is described as a hyperendemic area for coccidioidomycosis. In Tucson, Arizona, disseminated

coccidioidomycosis is the third most common AIDS-defining illness [2, 3]. In the endemic areas of Arizona, disseminated coccidioidomycosis accounted for 8.2% of all AIDS diagnoses [4]. There have been no California-specific studies of the impact of coccidioidomycosis on the HIV-infected population.

The following questions will help address these issues.

B. Questions

What is the overall prevalence of AIDS-defining coccidioidomycosis in California and in the hyperendemic regions of California?

The percentage of AIDS patients with disseminated coccidioidomycosis will give insight into the impact of coccidioidomycosis on the HIV-infected population.

How has AIDS-defining coccidioidomycosis changed over time in California?

Looking at the temporal trends of AIDS-defining coccidioidomycosis in California helps evaluate the idea that coccidioidomycosis is an emerging disease in California due to the HIV epidemic. AIDS-defining coccidioidomycosis has been a reportable disease for ten years and the AIDS registry may reflect movement of the HIV epidemic into areas endemic for coccidioidomycosis.

Is there a seasonal pattern to the occurrence of AIDS-defining coccidioidomycosis?

Coccidioidomycosis among patients without AIDS or HIV infections has a definite seasonal pattern. Since immunosuppressed patients may have symptomatic coccidioidomycosis by virtue of a newly acquired infection or by reactivation of a

latent infection, examining the monthly occurrence of reported cases of AIDS-defining coccidioidomycosis may give insight into the balance between these two types of presentations.

What was the effect of the coccidioidomycosis epidemic of 1991 to 1994 on the HIV-infected population?

The epidemic of coccidioidomycosis in California resulted in a huge increase in the number of cases of non-AIDS coccidioidomycosis but the effect on the HIV-infected population is not known.

What are the demographics and risk factors of AIDS-defining coccidioidomycosis?

Although a prospective study may be desirable to determine the impact of the different manifestations of coccidioidomycosis on the HIV-infected population, demographic characteristics and risk factors for coccidioidomycosis in HIV-infected people can be defined through reported cases of AIDS-defining coccidioidomycosis.

Methods

A. Data Collection

The Office of AIDS of the California Department of Health Services (CDHS), in cooperation with the Centers for Disease Control and Prevention (CDC), maintains a registry of all reported cases of AIDS in the state of California. The AIDS Reporting System (ARS), developed by the CDC and other organizations, is used on a national basis. Medical care providers are required to check all AIDS-defining conditions that apply to a patient at the time of report. In addition, health department personnel may provide case reports from review of hospital or other care facilities. Local health departments within the state submit these reports to the CDHS. Providers or local health departments are not required to report opportunistic infections following a diagnosis of AIDS, although some reporting of subsequent diagnoses does occur.

For each patient, multiple variables are recorded, including, in part, date of AIDS diagnosis, gender, race and ethnicity, age, probable mode of HIV transmission, county of residence at time of AIDS diagnosis, and specific AIDS-defining conditions.

B. Inclusion and Exclusion Criteria

CDC Case Definition for AIDS-Defining Coccidioidomycosis

For a case of AIDS-defining coccidioidomycosis to be eligible for this analysis, it must meet the 1987 CDC case definition. The AIDS surveillance definition, outlined in the 1987 revision of the CDC surveillance case definition for AIDS, defines disseminated

coccidioidomycosis as coccidioidomycosis at any site other than or in addition to the lungs or cervical or hilar lymph nodes with *C. immitis* identified by histology, cytology, culture or detection of antigen in a specimen obtained directly from the tissues affected or a fluid from those tissues [1].

Exclusion of Pre-1987 Cases

Since the beginning of 1987, cases of AIDS-defining coccidioidomycosis have been reported to the CDHS. Therefore inclusion into this analysis required that the diagnosis of AIDS have been made from 1987 through 1996 and as a result, 9,069 pre-1987 cases present in the data set were eliminated.

Exclusion of Cases of Unknown Status

The status of 38 cases of disseminated coccidioidomycosis was not clear due to missing information. These cases could have been AIDS-defining coccidioidomycosis or disseminated coccidioidomycosis contracted subsequent to a previous AIDS diagnosis. In all cases, the date of diagnosis of coccidioidomycosis was not recorded so it was not possible to determine if the case was AIDS-defining or a subsequent infection.

Exclusion of Other Cases Having Incomplete Data

Twenty-one cases of AIDS-defining coccidioidomycosis had an HIV transmission mode category of "risk not specified". Since this category represents incomplete data, these cases were eliminated. In addition, 3,183 cases of other AIDS-defining illnesses were eliminated for the same reason.

A total of 257 cases were removed from the analysis because no county of residence was recorded (11 cases) or no month of diagnosis was recorded (246 cases).

All of these were AIDS-defining conditions other than AIDS-defining coccidioidomycosis.

Total cases

After applying these criteria, 85,729 cases of AIDS were used in this analysis. Of these, 145 had disseminated coccidioidomycosis as their AIDS-defining illness.

C. Statewide Analysis

Temporal trends

In order to determine the effect of the epidemic in California during 1991 to 1994 as well as to evaluate the notion that coccidioidomycosis is an "emerging disease", cases of AIDS-defining coccidioidomycosis were evaluated for an increasing trend as a percentage of all AIDS cases over time.

Cases of AIDS-defining coccidioidomycosis were compared to cases of all other AIDS-defining conditions to investigate the effect of seasonality on the diagnosis of AIDS-defining coccidioidomycosis.

Univariate Demographic and Risk Factor Analysis

In the univariate analysis, cases of AIDS-defining coccidioidomycosis were compared to all other AIDS-defining conditions on the basis of race or ethnicity, age group, HIV transmission category and gender. Race or ethnicity groups were: Whites, Blacks, Hispanics and Other. The "other" group contained all other races or ethnicities. Ages were grouped to facilitate analysis as follows: less than 20 years, 20 to 29 years, 30

to 39 years, 40 to 49 years, 50 to 59 years, and 60 years and greater. The HIV transmission mode groups were: homosexual or bisexual males, injections drug users, homosexual or bisexual male injection drug users, heterosexual contact, and other. The "other" group contained HIV transmission categories that were documented (for example, blood transfusion) but were grouped together for ease of analysis.

Relationships within tables were investigated further by calculation of odds ratios.

D. Endemic Area Definition

County frequency

The frequency of AIDS-defining coccidioidomycosis by county was tabulated to determine a contiguous area of California in which cases of AIDS-defining coccidioidomycosis are the greatest percentage of all AIDS cases. This area is deemed the "endemic" area for AIDS-defining coccidioidomycosis. Note that this area will not correspond exactly to the endemic area of coccidioidomycosis since it is based on the borders of counties rather than environmental sites of *C. immitis*.

E. Endemic and Non-endemic Area Analysis

All AIDS cases were stratified based on whether they were reported in the defined endemic area versus the non-endemic area of California.

Temporal Trends

Similar to the statewide analysis, cases of AIDS-defining coccidioidomycosis are evaluated for a possible increasing trend in the proportion of all AIDS cases.

Univariate Demographic and Risk Factor Analysis

Similar to the statewide analysis, cases of AIDS-defining coccidioidomycosis are compared to all other AIDS cases within the endemic area on the basis of race or ethnicity, age group, HIV transmission category and gender. The same analysis was performed for the non-endemic area. Relationships within the tables are further examined by calculation of odds ratios.

Comparison of Cases of AIDS-defining Coccidioidomycosis From the Endemic Area to the Cases from the Non-endemic Area

Cases of AIDS-defining coccidioidomycosis from the endemic area are compared to cases of AIDS-defining coccidioidomycosis from the non-endemic area by calculation of risk ratios. The cases are compared on the basis of race or ethnicity, age group, HIV transmission category and gender.

F. Statistical Software and Data Management

Data management and statistical analysis was performed with PC-SAS [5].

Results

A. Prevalence

During the period from 1987 through 1996, 85,729 cases of AIDS met the inclusion criteria of this study. Of these 145 (0.17%) patients had disseminated coccidioidomycosis as their AIDS-defining condition and 85,584 (99.83%) had another condition as their AIDS-defining illness. In addition, there were 112 (0.13%) cases of disseminated coccidioidomycosis reported subsequent to a previous diagnosis of AIDS.

B. Statewide Analysis

Temporal

1. Year

Figure 1 shows the number of cases of AIDS-defining coccidioidomycosis reported each year in California for the period of 1987 through 1996. In addition, the percentage of all AIDS cases that these cases of AIDS-defining coccidioidomycosis comprises is also shown on the graph.

Cases of AIDS-defining coccidioidomycosis rose from a low of 4 in 1987 (0.07% of all AIDS cases) to a high of 29 in 1992 (0.23% of all AIDS cases). Following 1992, reported cases of AIDS-defining coccidioidomycosis began to decline down to 11 in 1996 (0.23% of all AIDS cases). The proportion of all AIDS patients having disseminated coccidioidomycosis as their AIDS-defining illness rose more than three-

fold over the ten-year period and this increase was statistically significant ($\chi^2 = 12.68$, $p < 0.001$).

2. Seasonality

Over the ten-year period, cases of AIDS-defining coccidioidomycosis ranged from a low of 8 in July to 18 reported for April (Figure 2). There was no statistical association between month of the year and AIDS-defining coccidioidomycosis ($\chi^2 = 13.17$, $p = 0.28$).

Within each year, cases appeared randomly by month, except during the epidemic years of 1991, 1992 and 1993. During these years, cases appeared in a manner more consistent with the seasonal pattern associated with non-AIDS-related coccidioidomycosis.

Demographic and Risk Factor Analysis

1. HIV Transmission Category

In the univariate analysis, mode of HIV transmission was strongly associated with AIDS-defining coccidioidomycosis ($\chi^2 = 18.45$, $p = 0.001$) (Table 1). Notable in this table is that homosexual or bisexual men appear to be under-represented among those patients with AIDS-defining coccidioidomycosis (89/145 cases, 61.4%) compared to homosexual or bisexual men among those patients presenting with all other AIDS-defining conditions (63,709/85,584 cases, 74.4%). Also injection drug users are over-represented among those patients with AIDS-defining coccidioidomycosis (30/145 cases, 20.7%) compared to those injection drug users presenting with all other AIDS-defining conditions (9,094/85,584 cases, 10.6%).

With homosexual or bisexual men used as the reference category, all other HIV transmission categories had odds ratios greater than the reference, but only the odds ratio (OR) for injection drug users was significant (OR = 2.36; 95% Confidence Interval [CI], 1.56 - 3.57).

2. Race/Ethnicity

In the univariate analysis, race or ethnicity was strongly associated with AIDS-defining coccidioidomycosis (χ^2 = 30.58, p = 0.001) (Table 2). Notable in this table is that Whites appear to be under-represented among those patients with AIDS-defining coccidioidomycosis (66/145 cases, 45.5%) compared to those patients presenting with all other AIDS-defining conditions (53,940/85,584 cases, 63.0%). Also Hispanics are over-represented among those patients with AIDS-defining coccidioidomycosis (51/145 cases, 35.2%) compared to those patients presenting with all other AIDS-defining conditions (15,484/85,584 cases, 18.1%).

Using Whites as the reference group, all other racial or ethnic groups had odds ratios greater than the reference, but only the odds ratio for Hispanics was significant (OR = 2.69; 95% CI, 1.87 - 3.88).

3. Age Group

There were no cases of AIDS-defining coccidioidomycosis among patients under 20 years old (Table 3). In the univariate analysis, age group was associated with AIDS-defining coccidioidomycosis (χ^2 = 13.19, p = 0.022). In particular, 40 to 49 year olds were under-represented among patients with AIDS-defining coccidioidomycosis. With 20 to 29 year olds as the reference category, all other age groups had odds ratios less than

the reference, but a significant finding occurred only with 40 to 49 year (OR = 0.46; 95% CI, 0.27 - 0.78).

4. Gender

Although males far outnumber females (145 cases versus 10 cases) among cases of AIDS-defining coccidioidomycosis, gender was not statistically associated with AIDS-defining coccidioidomycosis (χ^2 = 0.03, p = 0.865) (Table 4).

C. County Analysis

Definition of Endemic Area

1. County Frequency

Table 5 shows the frequency of AIDS-defining coccidioidomycosis for each county. Of the 57 counties in California that reported cases of AIDS over the period of 1987 through 1996, 21 reported cases of AIDS-defining coccidioidomycosis.

Kern, Tulare, Kings and San Luis Obispo Counties constituted a contiguous area of California with the highest percentage of AIDS cases due to a diagnosis of disseminated coccidioidomycosis and is defined as the endemic area for AIDS-defining coccidioidomycosis in California (Figure 3). Kern, Tulare, Kings and San Luis Obispo Counties reported 18, 3, 1 and 3 cases of AIDS-defining coccidioidomycosis, respectively, which correspond to 2.7%, 1.7%, 1.0% and 1.0% of all AIDS cases reported in the county, respectively. Overall, these 25 cases corresponded to 2.0% of all AIDS cases in these four counties.

These four counties reported 17.2% of the 145 cases of AIDS-defining coccidioidomycosis in California during the ten-year time period. The other 53 counties reported a total of 120 (82.8%) of the 145 cases of AIDS-defining coccidioidomycosis. This amounted to only 0.14% of all AIDS cases in those 53 counties. Using the non-endemic area (all other counties) as the reference group, the odds ratios associated with AIDS-defining coccidioidomycosis in the individual endemic counties are significant with the greatest for Kern County (OR = 19.47; CI, 11.79 - 32.14) (Table 6).

Although Imperial County had the third highest percentage of AIDS cases defined by a diagnosis of disseminated coccidioidomycosis (1.3%), it was not included in the endemic area definition because it is not contiguous with the four-county block. The greatest number of cases of AIDS-defining coccidioidomycosis were reported from Los Angeles County (38 cases), but this only accounted for 0.13% of the total number of AIDS cases reported in that county.

Endemic and Non-endemic Area Analyses

After stratifying based on region (endemic or non-endemic), it is immediately noticeable that the endemic area is very different from the non-endemic region in its demographic and risk factors for AIDS-defining coccidioidomycosis. The non-endemic area is very similar to the statewide. Separating the endemic area from the statewide group had little impact on the non-endemic area due to the endemic area's small size (only 1,253 total cases of AIDS over the ten-year period).

1. Temporal

There was only one case of AIDS-defining coccidioidomycosis reported in the endemic area prior to the beginning of the epidemic of coccidioidomycosis in California in 1991 (Figure 4). There was no evidence of a statistically increasing trend in the proportion of all AIDS cases reported in the endemic area, cases of AIDS-defining coccidioidomycosis ($\chi^2 = 2.14$, $p > 0.10$).

There was statistical evidence of an increasing trend in the proportion of patients with AIDS in the non-endemic area having their AIDS-defining illness due to disseminated coccidioidomycosis ($\chi^2 = 6.77$, $p < 0.01$) (Figure 5). During the epidemic years, 60% of all cases of AIDS-defining coccidioidomycosis from the non-endemic area were reported. In addition, the non-endemic area had a drop over time in the number of cases of AIDS in California since 1992.

2. HIV Transmission Category

In the univariate analysis for the endemic area, mode of HIV transmission was not associated with AIDS-defining coccidioidomycosis (Fisher's exact test, $p = 0.978$) (Table 7). With homosexual or bisexual men used as the reference category, all other HIV transmission categories had odds ratios similar to the reference, with none statistically significant.

In the univariate analysis for the non-endemic area, mode of HIV transmission was associated with AIDS-defining coccidioidomycosis ($\chi^2 = 14.37$, $p = 0.006$) (Table 7). Similar to the statewide analysis, homosexual or bisexual men are under-represented among those patients with AIDS-defining coccidioidomycosis (76/120 cases, 63.3%) compared to homosexual or bisexual men among those patients presenting with all other

AIDS-defining conditions (63,129/84,356 cases, 74.8%). Also injection drug users are over-represented among those patients with AIDS-defining coccidioidomycosis (24/120 cases, 20.0%) compared to those injection drug users presenting with all other AIDS-defining conditions (9,094/85,584 cases, 10.6%). With homosexual or bisexual men used as the reference category, all other HIV transmission categories had odds ratios greater than the reference, but only the odds ratio for injection drug users was significant (OR = 2.27; CI, 1.43 - 3.60).

3. Race/Ethnicity

In the univariate analysis for the endemic area, race or ethnicity was statistically associated with AIDS-defining coccidioidomycosis ($\chi^2 = 13.30$, $p = 0.004$) (Table 8). Similar to the statewide univariate analysis, Whites are under-represented among those patients with AIDS-defining coccidioidomycosis (9/25 cases, 36.0%) compared to those patients presenting with all other AIDS-defining conditions (671/1,228 cases, 54.6%). Also Hispanics are greatly over-represented with more than half of the cases of AIDS-defining coccidioidomycosis among Hispanics (13/25 cases, 52.0%). In contrast, Hispanics comprised less than one-fourth of all other AIDS-defining conditions in the endemic area (278/1,228 or 22.6%). Again using Whites as the reference group, Hispanics had almost two and a half times the odds of having disseminated coccidioidomycosis as their AIDS-defining illness compared to Whites (OR = 3.49; CI, 1.47 - 8.25).

In the univariate analysis in the non-endemic area, race or ethnicity was strongly associated with AIDS-defining coccidioidomycosis ($\chi^2 = 18.05$, $p = 0.001$) (Table 8). Similar to the statewide analysis, Whites are under-represented among those patients with

AIDS-defining coccidioidomycosis (57/120 cases, 47.5%) compared to those patients presenting with all other AIDS-defining conditions (53,269/84,356 cases, 63.2%). Also Hispanics are over-represented among those patients with AIDS-defining coccidioidomycosis (38/120 cases, 31.7%) compared to those patients presenting with all other AIDS-defining conditions (15,206/84,356 cases, 18.0%). Using Whites as the reference group, all other racial or ethnic groups had odds ratios greater than the reference, but only the odds ratio for Hispanics was significant (OR = 2.34; CI, 1.54 - 3.52).

4. Age Group

There were no cases of AIDS-defining coccidioidomycosis among patients under 20 years old (Table 9). Unlike the statewide univariate analysis, age group was not statistically associated with AIDS-defining coccidioidomycosis in the endemic area (Fisher's exact test, $p = 0.811$) and the non-endemic area ($\chi^2 = 9.21$, $p = 0.101$) (Table 9).

Using the 20 to 29 year old group as the reference, 40 to 49 year olds in the non-endemic area were associated with decreased risk of AIDS-defining coccidioidomycosis (OR = 0.48; CI, 0.27 - 0.85).

5. Gender

In the endemic region of California, only one woman was diagnosed with AIDS-defining coccidioidomycosis during the study period. Gender, however, was not statistically associated with AIDS-defining coccidioidomycosis (Fisher's exact test, $p = 1.00$) (Table 10).

Likewise, in the non-endemic area, gender was not statistically associated with AIDS-defining coccidioidomycosis (Fisher's exact test, $p = 0.581$) (Table 10).

Comparison of Cases by Region

Table 11 shows the comparison of the cases of AIDS-defining coccidioidomycosis from the endemic region to the cases of AIDS-defining coccidioidomycosis from the non-endemic region. There were no significant differences in the prevalence ratios between the two regions.

Discussion

A. Prevalence

At only 0.17% of all AIDS-defining conditions in California over the period of 1987 through 1996, disseminated coccidioidomycosis is a rare AIDS-defining condition. By comparison, *Pneumocystis carinii* pneumonia and Kaposi's sarcoma were the most common AIDS-defining conditions accounting for approximately 16% and 5%, respectively, of all AIDS cases during the same time period.

Possible Explanations for the Scarcity of Case Reports

It should be noted that the number of reported cases of AIDS-defining coccidioidomycosis in California must be considered a minimum for a number of reasons. First, coccidioidomycosis is considered an underreported disease [6]. Kern County's efficiency of reporting coccidioidomycosis is unique in California. Therefore, other counties may be underreporting. Outside the endemic areas a diagnosis of coccidioidomycosis may be more likely missed since care providers may have had little experience with this, a previously regional, disease. Akin to the under-reporting of non-AIDS coccidioidomycosis, particularly outside of the endemic areas, a diagnosis of AIDS-defining coccidioidomycosis may be more likely to be missed or not reported. Although there is heightened awareness of coccidioidomycosis due to the coccidioidomycosis epidemic and the resulting national reporting requirement in 1995, this may have only impacted the later years of this study period. With populations highly mobile and more people moving to the southwest, health care professionals need to be more aware of the possibility of coccidioidomycosis in HIV-positive persons.

The AIDS Reporting System primarily gathers information on AIDS-defining conditions. Infections following an initial AIDS-defining condition are not reliably reported. Thus, the 112 reported cases of disseminated coccidioidomycosis reported following the initial AIDS definition probably understate the magnitude of the impact of this disease.

In addition, only disseminated coccidioidomycosis, the least common form of coccidioidomycosis, is an AIDS-defining condition. As stated earlier, pulmonary manifestations of coccidioidomycosis are more common in HIV-infected individuals and are not AIDS-defining conditions. In particular, although it may present diagnostic and case definition difficulties, diffuse pulmonary disease is a presentation peculiar to HIV-infected people [3, 7, 8] and should be considered for inclusion in the case definition for AIDS-defining coccidioidomycosis because of its rapid mortality in this population.

Finally, the 1993 AIDS case definition revision included, among other things, the AIDS-defining condition based on a person's $CD4^+$ count. People infected with HIV who may have been defined as having AIDS due to an opportunistic infection may be defined as having AIDS based on a $CD4^+$ count of less than $0.200 \times 10^9/L$. A recent study showed the median $CD4^+$ count among HIV-positive patients who had active coccidioidomycosis was less than $0.100 \times 10^9/L$ [7]. The 1993 case definition has the result of blunting the full recognition of rarer opportunistic infections such as coccidioidomycosis. This is mentioned to highlight the need for a system that tracks subsequent opportunistic infections to accurately assess the impact of a disease like coccidioidomycosis on the HIV-positive population. Although AIDS-defining

coccidioidomycosis is a relatively rare occurrence, serious coccidioidomycosis among HIV-positive persons is not an uncommon disease.

California in Comparison to Arizona

Even in Kern County, the greatest area of endemicity for non-AIDS coccidioidomycosis in California, AIDS-defining coccidioidomycosis accounted for only 2.7% of all AIDS diagnoses over the ten-year period. This stands in contrast to the very significant finding that disseminated coccidioidomycosis accounted for 8.2% of all AIDS-defining conditions in endemic counties of Arizona from 1987 through 1992 [4].

This relative paucity of reports in California compared to Arizona may be related to four things. First, although the data in this study validate the notion that the HIV epidemic seems to be moving into areas more endemic for coccidioidomycosis, areas of Arizona may have a greater HIV-infected population compared to the hyperendemic areas for coccidioidomycosis in California. During 1990 through 1995, the prevalence of AIDS increased 79% in Arizona [9].

Second, as mentioned already, coccidioidomycosis is an under-reported disease in California. Third, non-AIDS and AIDS-defining coccidioidomycosis may be over-reported conditions in Arizona. Based on the greater volume of research coming out of Arizona, there is much greater awareness centered on coccidioidomycosis among HIV-infected patients in Arizona than there is in California. But an over-reporting phenomenon seems unlikely due to the strict case definition for AIDS-defining coccidioidomycosis (laboratory confirmation required). Lastly, the great difference in prevalence of AIDS-defining coccidioidomycosis between these two regions may be the

result of a true difference in factors that lead to an increased risk of symptomatic infection with *C. immitis.* Arizona may have a greater concentration of *C. immitis* in endemic areas or California may have a less recently immigrated population that has greater pre-existing immunity to coccidioidomycosis.

B. Temporal Aspects of AIDS-defining Coccidioidomycosis

Statewide

1. Year

Most of the cases of AIDS-defining coccidioidomycosis were reported during the period of 1991 through 1994. This parallels the epidemic of non-AIDS coccidioidomycosis in California denoting the effect of the epidemic on the HIV-infected population. The increase in cases of AIDS-defining coccidioidomycosis undoubtedly arose during this time because the bloom of *C. immitis* led to greater innocula and a corresponding increase in the chance of infection in HIV-infected persons.

Although reported cases of AIDS-defining coccidioidomycosis declined following the peak of the epidemic in 1992, the percentage of all AIDS cases defined by a diagnosis of disseminated coccidioidomycosis remained elevated through 1996 in comparison to the pre-epidemic years. While the number of cases of AIDS-defining coccidioidomycosis declined following the epidemic, the total number of AIDS cases declined more rapidly. With greater knowledge of HIV disease management and prophylaxis, HIV-infected patients may be living longer without AIDS-defining illnesses, but an environmental occurrence, such as the epidemic, can have a profound effect on

this population. The increased awareness of coccidioidomycosis due to the epidemic years may also be influential on the increasing trend in the proportion AIDS cases as a result of disseminated coccidioidomycosis.

In addition, the increase in cases reflects the movement of the HIV epidemic into areas endemic for coccidioidomycosis.

2. Seasonality

Although the reporting of cases of AIDS-defining coccidioidomycosis appears to parallel the epidemic of non-AIDS coccidioidomycosis, the seasonal aspects of reporting are not as clear. If all cases were due to new infections, then most cases would appear in late fall and early winter. If all cases of AIDS-defining coccidioidomycosis were due to reactivation of latent infection, cases would appear uniformly throughout the year. Coccidioidomycosis in HIV-infected people is known to be due to both new infections and reactivation of a previous infection, although the proportion is not clear.

Investigating this issue by looking at the seasonal aspects of reported cases is probably complicated by infections that may result from a lower required innoculum in HIV-infected people. That is, if immunosuppressed persons become infected at a lower innoculum, then they are more likely than immunocompetent persons to be infected during times of the year that are associated with less *C. immitis*. Thus, cases of coccidioidomycosis in HIV-infected individuals are likely to appear at any time of the year.

Knowledge of the proportion of new cases versus reactivated cases is useful as this potentially could have an impact on the treatment or prophylaxis of HIV-infected

patients. For example, if HIV-infected patients with latent coccidioidomycosis are at risk for reactivation at a certain $CD4^+$ count, prophylaxis or close monitoring may be helpful.

The lack of association between month and AIDS-defining coccidioidomycosis highlights the difficulty in sorting out the mechanism of symptomatic infection in HIV-infected patients. To accurately assess this issue, information on a previous infection by *C. immitis* must be available.

Endemic and Non-endemic Areas

1. Year

Four counties (Kern, Kings, San Luis Obispo and Tulare) have the greatest percentage of AIDS cases defined by a diagnosis of disseminated coccidioidomycosis. This endemic area, however, did not show an increasing trend in the proportion of AIDS cases defined by a diagnosis of disseminated coccidioidomycosis over the ten-year period. Interestingly, there was only one case of AIDS-defining coccidioidomycosis reported in the endemic area prior to 1991. The vast majority of cases in the endemic area (24 out of 25 total cases) appeared during the epidemic years. So the epidemic appears to be strongly related to the increase of cases of AIDS-defining coccidioidomycosis in the endemic area.

There was a corresponding increase in all AIDS cases in this area (in the four endemic counties, reported AIDS cases rose more than 300% from 1987 to 1992). This is more support for the idea that the HIV epidemic is moving into rural areas that are also endemic for coccidioidomycosis. Although the endemic area reports few cases of AIDS, only 1,253 cases of AIDS reported over the ten-year period (1.5% of all AIDS cases), a

continued movement of the HIV epidemic to this area will likely result in more cases of AIDS-defining coccidioidomycosis. Although HIV-infected people should not be discouraged from living in endemic areas for coccidioidomycosis, they should be aware of the seasonal aspects of coccidioidomycosis as well as its epidemic potential.

Similar to the statewide analysis, it appears that the rise in cases in the non-endemic area parallels the events in the non-AIDS coccidioidomycosis epidemic, although not as dramatically as that of the endemic area. Since the reporting of cases in the non-endemic area looks to be dominated by the epidemic years (that is, new infections), this may imply that the boundaries of the endemic area defined in this study may not accurately reflect the true endemic area for coccidioidomycosis in California.

2. Seasonality

Visually, cases of AIDS-defining coccidioidomycosis in the endemic area more closely matched the seasonal pattern for non-AIDS coccidioidomycosis, but there was no statistical association between month and AIDS-defining coccidioidomycosis. Similar to the reasons outlined for the statewide analysis, a non-seasonal pattern to reported cases might result from reactivation of latent infection or a decreased required innoculum due to immunosuppression. This same comment applies to the non-endemic area.

C. Demographic and Risk Factor Analysis

HIV Transmission Category

In the statewide and non-endemic groups, HIV transmission mode was strongly associated with AIDS-defining coccidioidomycosis and injection drug users were over-

represented among patients with AIDS-defining coccidioidomycosis. Although this has been reported for injection drug users in endemic counties of the United States [4], there was no such association in the four-county endemic area of this study. The reason for the difference in these findings may lie in the definitions of endemic areas. Jones and colleagues [4] presumably used all counties from the United States that are endemic for *C. immitis* whereas this study identified an endemic area based on the proportion of all patients having disseminated coccidioidomycosis as their AIDS-defining illness.

The reasons for over-representation of injection drug users in the non-endemic area is not clear. Jones and colleagues [4] speculated that this association could be related to more exposure to coccidioidomycosis via soil exposure in injecting drug users through occupation, residential conditions or other factors. In a discussion of disease progression in different HIV-positive groups, Gardner and colleagues [10] noted that injection drug users often do not have access to regular medical care. When this disparity is absent, such as in the military cohort they studied, there is no difference in HIV progression between transmission groups. Perhaps less frequent care leads injection drug users in the non-endemic area to be more susceptible to AIDS-defining coccidioidomycosis.

Racial/Ethnic Groups

Blacks are known to have 10 times the rate of disseminated coccidioidomycosis than Whites [11, 12]. In this study, Blacks in the non-endemic and statewide analysis were not differentially represented among AIDS-defining coccidioidomycosis and all other AIDS-defining conditions. Again, this makes sense in the context of the proposed mechanism for dissemination among racial categories. Jones and colleagues [4] reported a similar result and hypothesized that once immunosuppressed, non-Black persons are

just as likely to have disseminated disease as Black persons. In the endemic area, however, few Blacks were reported with AIDS-defining coccidioidomycosis, but there was no statistical significance to this finding in comparison to the reference group (Whites).

Contrary to the findings among Blacks, Hispanics were over-represented in the statewide and both regional analyses. Whether immunocompetent Hispanics are at increased risk for disseminated coccidioidomycosis is not clear as authors are currently challenging the long-held belief that the racial predilection for disseminated coccidioidomycosis includes Hispanics. Again, the immune defect for disseminated disease is not related to a quantitative defect in immunocompetent individuals, so the over-representation of Hispanics in this study may be more likely due to some confounding influence on the relationship between Hispanics in California and coccidioidomycosis. The AIDS registry does not keep information on coccidioidomycosis-specific risk factors, such as occupation. In particular, agricultural occupations may be very relevant in the case of Hispanics and coccidioidomycosis [13]. It has been suggested that HIV-positive individuals should avoid occupations that possibly increase their exposure to *C. immitis*. Therefore, collecting information on occupation or exposure factors to dust would be useful from a public health standpoint to better define the risks for coccidioidomycosis associated with certain occupations.

Age

Only in the statewide analysis was age group associated with AIDS-defining coccidioidomycosis. Why 40 to 49 year olds are under-represented among AIDS patients with disseminated coccidioidomycosis is not clear. The risk of disseminated

coccidioidomycosis increases with age and this can be thought of as a form of relative immunosuppression. That is, age as a risk factor for disseminated coccidioidomycosis is unlike the relationship of race or gender with disseminated coccidioidomycosis. The increased risk of disseminated coccidioidomycosis associated with certain race or gender is not related to a relative immunosuppression, as it is in older patients. It would make sense that older patients with HIV would have increased rates of disseminated coccidioidomycosis compared to older patients with non-AIDS coccidioidomycosis. Older patients in this study, however, appear to be less likely to have disseminated coccidioidomycosis as their AIDS-defining illness compared to all other AIDS-defining conditions.

Older age in endemic counties of the United States was found to be protective in terms of having disseminated coccidioidomycosis as an AIDS-defining condition [4], but no clear reason for this finding was reported. This may have to do with a beneficial effect of previous immunity to coccidioidomycosis (the longer one lives in an endemic area, the more likely one will have been infected and developed immunity). This has some support in this study since most cases appear to be new infections, rather than reactivation of latent disease. Although there is no association between age group and AIDS-defining coccidioidomycosis in the four-county endemic area, all cases occurred between 20 and 49 years of age and there is a pattern suggestive of older patients having coccidioidomycosis less often than younger patients.

The frequency of disseminated disease was shown to be increased if a patient is 5 years of age or younger, or at least 50 years of age [14]. In this study, however, there were no cases of AIDS-defining coccidioidomycosis in patients less than 20 years old

and greater than 50 years old. In sum, the effect of age on the likelihood of presenting with disseminated coccidioidomycosis as an AIDS-defining condition remains very unclear.

Gender

Males are generally felt to be at increased risk for disseminated coccidioidomycosis [11]. Among the AIDS patients in this study no relationship between gender and AIDS-defining coccidioidomycosis was found and this finding supports a similar study of AIDS-defining coccidioidomycosis in endemic areas of the United States [4]. Again the postulated immune defect in disseminated coccidioidomycosis among immunocompetent hosts is not related to a quantitative defect as happens with HIV disease.

D. Comparison of Endemic Area Cases to Non-endemic Area Cases

The comparison of cases of AIDS-defining coccidioidomycosis from the endemic area and the non-endemic area showed no differences. The method used to define the endemic area in this study was based on a contiguous area of California that had an increased percentage of AIDS patients with disseminated coccidioidomycosis as their AIDS-defining illness. While the univariate analyses shows the endemic and non-endemic areas have different proportions of demographic and risk factors, the presence of *C. immitis* obviously has nothing to do with county boundaries and the definition of an endemic area is far complicated than any county-level stratification could represent.

Conclusions

The aim of this study was to describe the epidemiology of AIDS-defining coccidioidomycosis in California. Although disseminated coccidioidomycosis as an AIDS-defining opportunistic infection is rare in California, it appears that the HIV epidemic is moving into areas endemic for coccidioidomycosis. The future ramifications of this may be substantial, particularly if epidemic conditions exist. A continued increase in the percentage of AIDS patients having their AIDS status defined by disseminated coccidioidomycosis is likely to continue with the movement of new, susceptible individuals to endemic areas. Public health measures should be taken to ensure individuals infected with HIV are adequately informed about coccidioidomycosis, particularly if they are living or visiting an endemic area.

The mechanisms involved in the development of disseminated coccidioidomycosis in HIV-infected individuals are known, but the frequencies of new infections and reactivation of latent infections still remains unclear. This study, however, showed a strong relationship between the increase in cases of AIDS-defining coccidioidomycosis and the epidemic years. Although reactivation of latent infection is likely and documented, it is probably not as common as new infections. The benefit of immunity to coccidioidomycosis prior to infection with HIV has not been addressed in California.

The rarity of AIDS-defining coccidioidomycosis made it a difficult entity to study. Aside from the univariate analyses, the small numbers of cases involved made it difficult to evaluate the relationships between risk factors ands demographic characteristics. Besides Hispanic race, the endemic area defined in this study showed

little difference between those patients with AIDS-defining coccidioidomycosis and those with all other AIDS-defining conditions. In hyperendemic areas, immunosuppression may obliterate racial or other predilections of disseminated coccidioidomycosis.

Finally, study of coccidioidomycosis in HIV-infected people in California is just beginning. This study focused on a small part of the impact of coccidioidomycosis on the HIV-infected population, that is, disseminated coccidioidomycosis as an AIDS-defining condition. The epidemics of HIV and coccidioidomycosis in California have provided renewed impetus to study this disease and further epidemiological research will undoubtedly occur. This may provide further insights into a disease inextricably linked to common environmental events and the people most likely affected by these events: HIV-infected individuals.

Chapter Two References

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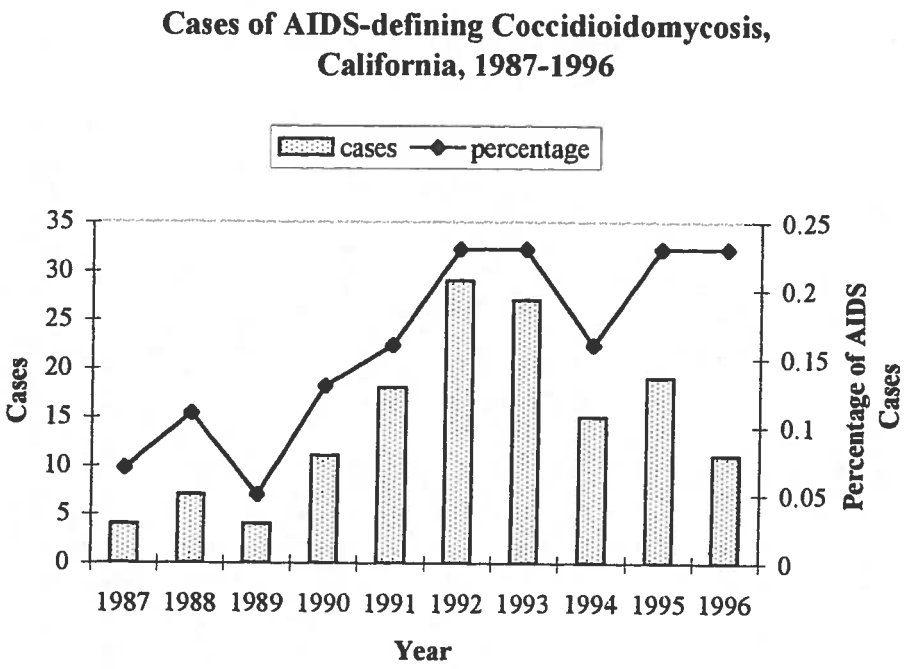

Figure 1. Cases of AIDS-Defining Coccidioidomycosis in California, 1987 – 1996.

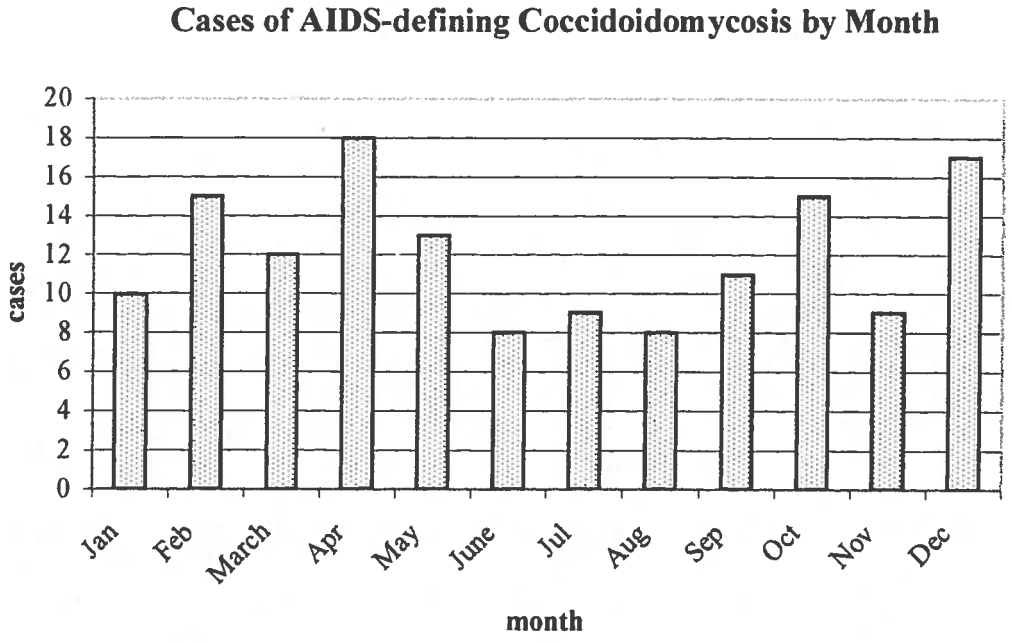

Figure 2: Cases of AIDS-Defining Coccidioidomycosis by Month of Diagnosis, California, 1987 - 1996

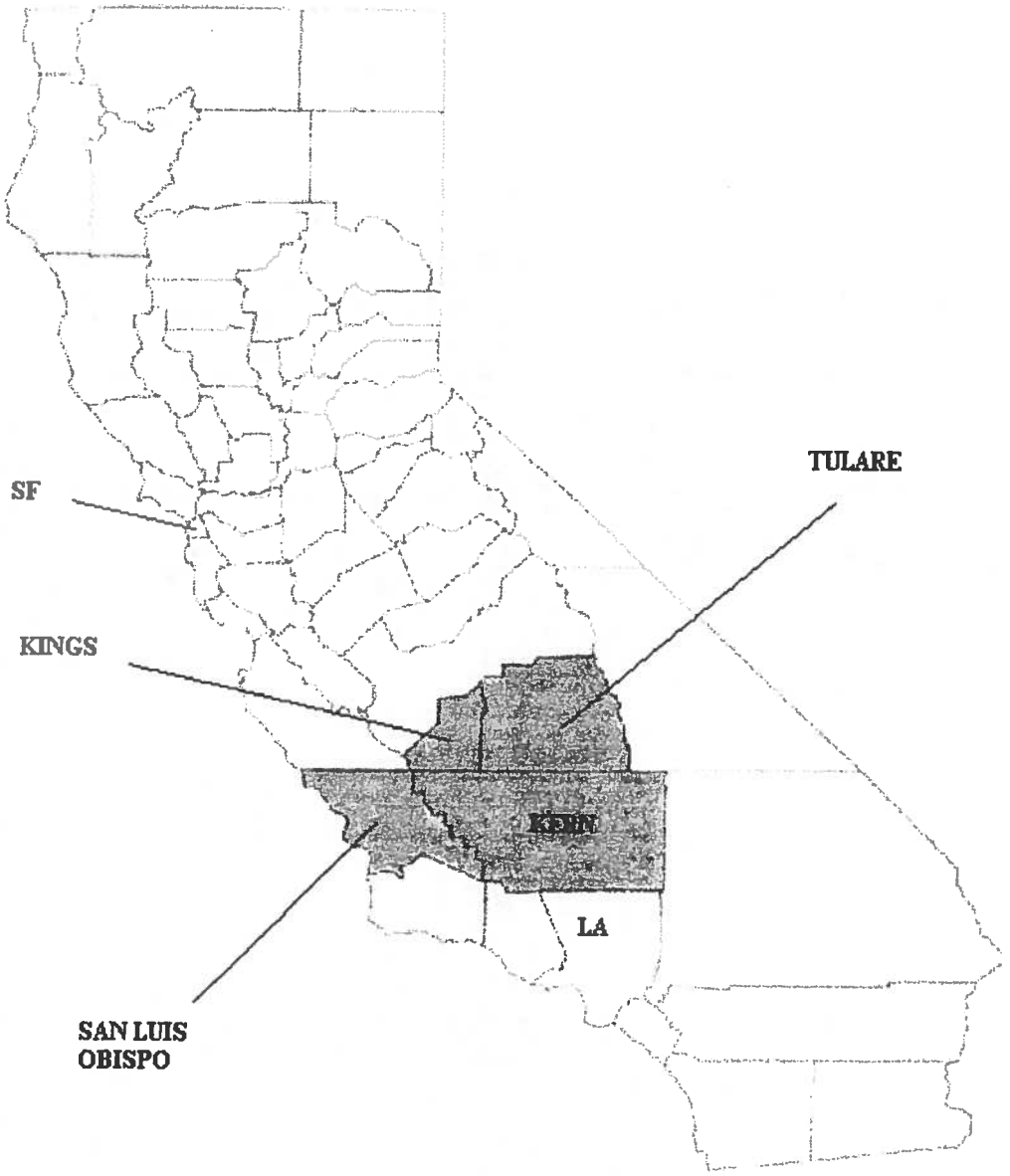

Figure 3: Endemic Area (shaded) of California for AIDS-Defining Coccidioidomycosis

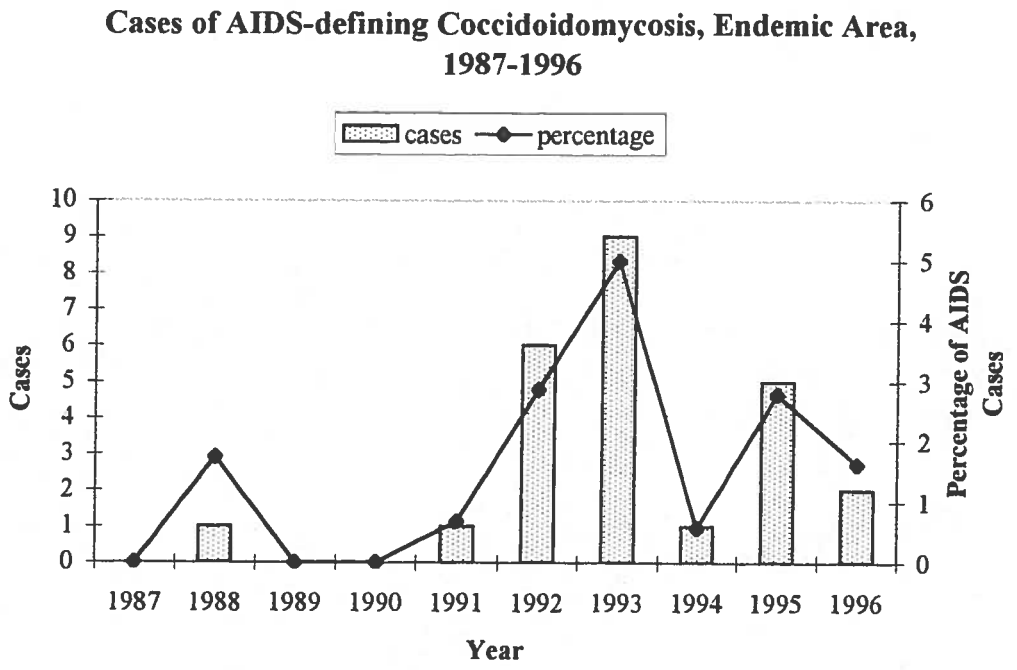

Figure 4. Cases of AIDS-Defining Coccidioidomycosis, Endemic Area of California, 1987 – 1996.

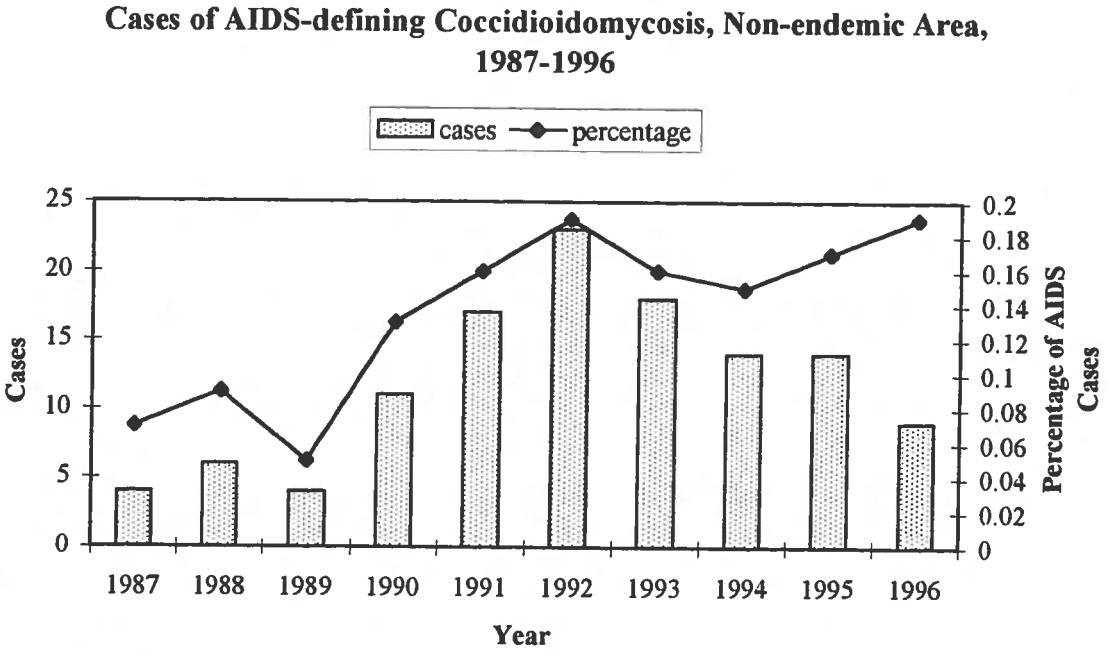

Figure 5. Cases of AIDS-Defining Coccidioidomycosis, Non-endemic Area of California, 1987 - 1996

Table 1. AIDS-Defining Coccidioidomycosis in California, 1987-1996, by HIV Transmission Category

Transmission Category	AIDS-defining Coccidioidomycosis (%)*	Other AIDS (%)*	OR (95% Confidence Interval)
Homo/Bisexual Male	89 (61.4%)	63709 (74.4%)	1.00 (ref)
Injection Drug Users (IDU)	**30 (20.7%)**	**9094 (10.6%)**	**2.36 (1.56, 3.57)**
Homo/Bisexual Male and IDU	13 (9.0%)	7179 (8.4%)	1.30 (0.72, 2.32)
Heterosexual	8 (5.5%)	3429 (4.0%)	1.67 (0.81, 3.45)
Other	5 (3.4%)	2173 (2.5%)	1.65 (0.67, 4.06)
Total	145 (100%)	85584 (100%)	

$\chi^2 = 18.45$; $p = 0.001$
* Column percentage

Table 2. AIDS-Defining Coccidioidomycosis in California, 1987-1996, by Race/Ethnicity

Race/Ethnicity	AIDS-defining Coccidioidomycosis (%)*	Other AIDS (%)*	OR (95% Confidence Interval)
White	66 (45.5%)	53940 (63.0%)	1.00 (ref)
Black	25 (17.2%)	13941 (16.3%)	1.47 (0.92, 2.32)
Hispanic	**51 (35.2%)**	**15484 (18.1%)**	**2.69 (1.87, 3.88)**
Other	3 (2.0%)	2219 (2.6%)	1.10 (0.35, 3.52)
Total	145 (100%)	85584 (100%)	

$\chi 2 = 30.58$, $p = 0.001$
* Column percentage

Table 3. AIDS-Defining Coccidioidomycosis in California, 1987-1996, by Age Group

Age Group	AIDS-defining Coccidioidomycosis (%)*	Other AIDS (%)*	OR (95% Confidence Interval)
< 20	0 (0.0%)	692 (0.9%)	0.31 (0.02, 5.08)**
20-29	31 (21.4%)	13326 (15.6%)	1.00 (ref)
30-39	77 (53.1%)	38613 (45.1%)	0.86 (0.56, 1.30)
40-49	**25 (17.2%)**	**23254 (27.2%)**	**0.46 (0.27, 0.78)**
50-59	10 (6.9%)	7186 (8.4%)	0.60 (0.29, 1.22)
60+	2 (1.4%)	2515 (2.9%)	0.34 (0.09, 1.37)
Total	145 (100%)	85584 (100%)	

$\chi 2 = 13.19$, $p = 0.022$

* Column percentage

** OR calculated using 0.5 instead of 0.

Table 4. AIDS-Defining Coccidioidomycosis in California, 1987-1996, by Gender

Gender	AIDS-defining Coccidioidomycosis (%)*	Other AIDS (%)*	OR (95% Confidence Interval)
Male	135 (93.1%)	79981 (93.5%)	1.00 (ref)
Female	10 (6.9%)	5603 (6.6%)	1.06 (0.56, 2.01)
Total	145 (100%)	85584 (100%)	

$\chi 2 = 0.029$, $p = 0.865$
* Column percentage

Table 5. Cases of AIDS-Defining Coccidioidomycosis as a Percentage of AIDS Cases in California Counties, 1987-1996

Endemic County	AIDS-defining Coccidioidomycosis (%)*	Other AIDS (%)*	Total AIDS Cases
Kern	18 (2.7%)	650 (97.3%)	668
Tulare	3 (1.7%)	171 (98.3%)	174
Kings	1 (1.0%)	98 (99.0%)	99
San Luis Obispo	3 (1.0%)	309 (99.0%)	312
Total	25	1228	1253

Non-Endemic County	AIDS-Defining Coccidioidomycosis (%)*	Other AIDS (%)*	Total AIDS Cases
Imperial	1 (1.3%)	79 (98.7%)	80
San Bernadino	12 (0.6%)	1997 (99.4%)	2009
San Joaquin	3 (0.6%)	537 (99.4%)	540
Ventura	2 (0.4%)	574 (99.6%)	576
Riverside	10 (0.3%)	2934 (99.7%)	2944
San Diego	23 (0.3%)	7754 (99.7%)	7777
Stanislaus	1 (0.3%)	394 (99.7%)	395
Solano	2 (0.2%)	822 (99.8%)	824
Fresno	2 (0.2%)	838 (99.8%)	840
Los Angeles	38 (0.1%)	29212 (98.9%)	29250
Orange	5 (0.1%)	4073 (99.9%)	4078
Contra Costa	2 (0.1%)	1649 (99.9%)	1651
Alameda	4 (0.1%)	4161 (99.9%)	4165
Santa Clara	2 (0.1%)	2300 (99.9%)	2302
Marin	1 (0.1%)	1150 (99.9%)	1151
San Francisco	11 (0.1%)	18075 (99.9%)	18086
Sacramento	1 (0.1%)	2126 (99.9%)	2127
All others (36 counties)	0 (0.0%)	5681 (100.0%)	5681
total	120	84356	84476

* Row Percentage (percentage of all AIDS cases in the county)

Table 6. Comparison of Endemic Counties of California to the Non-Endemic Area, California, 1987 – 1996.

County	AIDS-defining Coccidioidomycosis (%)*	Other AIDS (%)*	Total AIDS Cases	OR (95% Confidence Interval)
Kern	18 (2.7%)	650 (97.3%)	668	19.47 (11.8, 32.14)
Tulare	3 (1.7%)	171 (98.3%)	174	12.33 (3.88, 39.16)
Kings	1 (1.0%)	98 (99.0%)	99	7.17 (0.99, 51.85)
San Luis Obispo	3 (1.0%)	309 (99.0%)	312	6.82 (2.16, 21.58)
Non-endemic	120 (0.1%)	84356 (99.9%)	84476	1.00 (ref)
total	145	85584	85729	

* Row Percentage (percentage of all AIDS cases in the county)

Table 7. AIDS-Defining Coccidioidomycosis in the **Endemic** and **Non-Endemic** Regions of California, 1987-1996, by HIV Transmission Category

Endemic Region

Transmission Category	AIDS-defining Coccidioidomycosis (%)*	Other AIDS (%)*	OR (95% Confidence Interval)
Homo/Bisexual Male	13 (52.0%)	580 (47.2%)	1.00 (ref)
Injection Drug Users (IDU)	6 (24.0%)	316 (25.7%)	0.85 (0.32, 2.25)
Homo/Bisexual Male and IDU	4 (16.0%)	213 (17.4%)	0.84 (0.27, 2.60)
Heterosexual	2 (8.0%)	84 (6.8%)	1.06 (0.24, 4.79)
Other	0 (0.0%)	35 (2.9%)	0.67 (0.04, 10.97)
Total	25 (100%)	1228 (100%)	

Fisher's exact test; p = 0.978
* Column percentage

Non-Endemic Region

Transmission Category	AIDS-defining Coccidioidomycosis (%)*	Other AIDS (%)*	OR (95% Confidence Interval)
Homo/Bisexual Male	76 (63.3%)	63129 (74.8%)	1.00 (ref)
Injection Drug Users (IDU)	**24 (20.0%)**	**8778 (10.4%)**	**2.27 (1.43, 3.60)**
Homo/Bisexual Male and IDU	9 (7.5%)	6966 (8.3%)	1.07 (0.54, 2.14)
Heterosexual	6 (5.0%)	3345 (4.0%)	1.49 (0.65, 3.42)
Other	5 (4.2%)	2138 (2.5%)	1.94 (0.77, 4.81)
Total	120 (100%)	84356 (100%)	

$\chi 2 = 14.37$; p = 0.006
* Column percentage

Table 8. AIDS-Defining Coccidioidomycosis in the **Endemic** and **Non-Endemic** Regions of California, 1987-1996, by Race/Ethnicity

Endemic Region

Race/Ethnicity	AIDS-defining Coccidioidomycosis (%)*	Other AIDS (%)*	OR (95% Confidence Interval)
White	9 (36.0%)	671 (54.6%)	1.00 (ref)
Black	2 (8.0%)	257 (20.9%)	0.58 (0.12, 2.70)
Hispanic	**13 (52.0%)**	**278 (22.6%)**	**3.49 (1.47, 8.24)**
Other	1 (4.0%)	22 (1.8%)	3.39 (0.41, 27.9)
Total	25 (100%)	1228 (100%)	

$\chi 2 = 13.30$, $p = 0.004$
* Column percentage

Non-Endemic Region

Race/Ethnicity	AIDS-defining Coccidioidomycosis (%)*	Other AIDS (%)*	OR (95% Confidence Interval)
White	57 (47.5%)	53269 (63.2%)	1.00 (ref)
Black	23 (19.2%)	13684 (16.2%)	1.57 (0.97, 2.55)
Hispanic	**38 (31.7%)**	**15206 (18.0%)**	**3.49 (1.47, 8.24)**
Other	2 (1.7%)	2197 (2.6%)	0.85 (0.21, 3.49)
Total	120 (100%)	84356 (100%)	

$\chi 2 = 18.05$, $p = 0.001$
* Column percentage

Table 9. AIDS-Defining Coccidioidomycosis in the **Endemic** and **Non-Endemic** Regions of California, 1987-1996, by Age Group

Endemic Region

Age Group	AIDS-defining Coccidioidomycosis (%)*	Other AIDS (%)*	OR (95% Confidence Interval)
< 20	0 (0.0%)	9 (0.7%)	2.44 (0.13, 47.02)**
20-29	6 (24.0%)	263 (21.4%)	1.00 (ref)
30-39	15 (60.0%)	607 (49.4%)	1.08 (0.41, 2.82)
40-49	4 (16.0%)	254 (20.7%)	0.69 (0.19, 2.47)
50-59	0 (0.0%)	74 (6.0%)	0.30 (0.01, 5.36)
60+	0 (0.0%)	21 (1.7%)	1.04 (0.06, 17.24)
Total	25 (100%)	1228 (100%)	

Fisher's exact test, p = 0.811
* Column percentage

Non-Endemic Region

Age Group	AIDS-defining Coccidioidomycosis (%)*	Other AIDS (%)*	OR (95% Confidence Interval)
< 20	0 (0.0%)	683 (0.7%)	0.38 (0.02, 6.29)**
20-29	25 (20.8%)	13063 (15.5%)	1.00 (ref)
30-39	62 (51.7%)	38006 (45.1%)	0.85 (0.54, 1.36)
40-49	**21 (17.5%)**	**23000 (27.3%)**	**0.47 (0.27, 0.85)**
50-59	10 (8.3%)	7112 (8.4%)	0.73 (0.35, 1.53)
60+	2 (1.7%)	2492 (3.0%)	0.42 (0.10, 1.68)
Total	120 (100%)	84356 (100%)	

$\chi 2 = 9.21$, p = 0.101
* Column percentage
** OR calculated using 0.5 instead of 0.

Table 10. AIDS-Defining Coccidioidomycosis in the **Endemic** and **Non-Endemic** Regions of California, 1987-1996, by Gender

Endemic Region

Gender	AIDS-defining Coccidioidomycosis (%)*	Other AIDS (%)*	OR (95% Confidence Interval)
Male	24 (96.0%)	1136 (92.5%)	1.00 (ref)
Female	1 (4.0%)	92 (7.5%)	0.51 (0.07, 3.72)
Total	25 (100%)	1228 (100%)	

Fisher's exact test, p = 1.00
* Column percentage

Non-Endemic Region

Gender	AIDS-defining Coccidioidomycosis (%)*	Other AIDS (%)*	OR (95% Confidence Interval)
Male	111 (92.5%)	78845 (93.5%)	1.00 (ref)
Female	9 (7.5%)	5511 (6.5%)	1.16 (0.59, 2.28)
Total	145 (100%)	84356 (100%)	

Fisher's exact test, p = 0.581
* Column percentage

Table 11. Comparison of Cases of AIDS-Defining Coccidioidomycosis from the Endemic Region to Cases of AIDS-Defining Coccidioidomycosis from the Non-Endemic Region of California, 1987-1996, by Demographic and HIV Transmission Categories

	Endemic (%)	Non-endemic (%)	RR* (95% Confidence Interval)
Transmission Category			
Homo/Bisexual Male	13 (52.0%)	76 (63.3%)	0.82 (0.40, 1.67)
Injection Drug Users (IDU)	6 (24.0%)	24 (20.0%)	1.20 (0.53, 2.74)
Homo/Bisexual Male and IDU	4 (16.0%)	9 (7.5%)	2.13 (0.86, 5.27)
Heterosexual	2 (8.0%)	6 (5.0%)	1.60 (0.46, 5.62)
Other	0 (0.0%)	5 (4.2%)	0.00
Race/Ethnicity			
White	9 (36.0%)	57 (47.5%)	0.76 (0.36, 1.60)
Black	2 (8.0%)	23 (19.2%)	0.42 (0.11, 1.66)
Hispanic	13 (52.0%)	38 (31.7%)	1.64 (0.81, 3.33)
Other	1 (4.0%)	2 (1.7%)	2.42 (0.47, 12.49)
Age Group			
< 20 years	0 (0.0%)	0 (0.0%)	0.00
20-29 years	6 (24.0%)	25 (20.8%)	1.15 (0.50, 2.64)
30-39 years	15 (60.0%)	62 (51.7%)	1.16 (0.56, 2.41)
40-49 years	4 (16.0%)	21 (17.5%)	0.91 (0.34, 2.43)
50-59 years	0 (0.0%)	10 (8.3%)	0.00
60+	0 (0.0%)	2 (1.7%)	0.00
Gender			
Male	24 (96.0%)	111 (92.5%)	1.03 (0.15, 6.90)
Female	1 (4.0%)	9 (7.5%)	0.53 (0.08, 3.55)

* Risk Ratio