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# Interdisciplinary Science to Confront Coccidioidomycosis

Nikias Sarafoglou[1], Rafael Laniado-Laborin[2], William A. Sprigg[3], & Menas Kafatos[4]

[1] George Mason University, Arlington, Virginia, USA

[2] Universidad Autónoma de Baja California, Tijuana, Mexico

[3] University of Arizona, Tuscon, Arizona, USA

[4] Chapman University, Orange, California, USA

Correspondence: Nikias Sarafoglou, George Mason University, Arlington, Virginia, USA. E-mail: nsarafog@gmu.edu

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**Abstract**

The long journey of research to lower risks of Coccidioidomycosis (CM) began in the late 19th century in Argentina and continued north to Mexico, the US and other countries. During this trip, medical science led the way. Although interdisciplinary research is not alien to medical science, e.g. geographic epidemiology, interaction with other disciplines has been low priority.

This paper argues that the efficacy of CM mitigation and treatment can be improved through multi- and inter-disciplinary information exchange, particularly with earth and environmental sciences. Greater interaction and open publication practice are essential.

Section 1 describes CM-epidemiology, the clinical features, the diagnosis and finally, the treatment.

Section 2 discusses epidemiological evidence for atmospheric influence on cases of CM.

Section 3 highlights the most important contributions and controversies in the history of CM-research through scientometric or bibliometric evaluations of research that are based on Garfield's work on the propagation of scientific thinking.

**Keywords:** Coccidioidomycosis, Valley fever, epidemiology, fungal infection, disseminated, azoles, bibliometrics, spatio-temporal analysis, airborne dust, atmospheric models.

**Prologue**

> *"Illnesses do not come upon us out to the blue. They are developed from small daily sins against Nature. When enough sins have accumulated, illnesses will suddenly appear."* Hippocrates

In the history of humanity, epidemics and pandemics played a significant role for the demographics of the world population. Homer in his Iliad 3,000 years ago, describes the effects of the Trojan war epidemics. The historian Thucydides in his "History of the Peloponnesian War 2,500 years ago, explained systematically the miserabile visum of the classic Athens during the epidemics of this war.

"*Words indeed fail one when one tries to give a general picture of this disease; and as for the sufferings of individuals, they seemed almost beyond the capacity of human nature to endure."*

In the modern times new authors made great contributions for public understanding of epidemics:

Daniel Defoe's "A Journal of the Plague Year (1722)

Thomas Mann's "Der Tod in Venedig" (1912)

Albert Camus' "La peste" (1947)

Humanity's first lines of defense, cure and prevention are called into play: epidemiology, virology, medical science and hospital care. However focused and coordinated these scientists and practitioners may be, the link between onset and severity of the epidemics and atmospheric conditions appears missing from overall strategy and tactics.

We have found that different disciplines are based on often dissimilar scientific paradigms. For example, atmospheric sciences accept "Chaos Theory" as part of the forecast system. Medicine is a science based on "Determinism." When disciplines engage together over time on a grand challenge, ideas are shared, and solutions arrive faster.

The following manuscript informs us, via study of Coccidioidomycosis, why the net of interdisciplinary science should be cast further so that the linkages between atmospheric conditions and epidemics may be explained. Atmospheric scientists, geologists and mycologists have joined to produce models and analytical tools to anticipate risks of Valley fever contagion and to examine past incidents of disease outbreaks. The case is raised, briefly, of another interdisciplinary study applied to airborne dust and Meningitis across the African Sahel. For Coccidioidomycosis, knowing the source and spread of airborne particulates is critical.

## 1. Coccidioidomycosis: A Medical Perspective

### *1.1 Introduction*

The genus Coccidioides consists of two species: *C. immitis* and *C. posadasii*. Initially, it was believed that *C. immitis* was a species that existed only in California, while *C. posadasii* was the predominant species everywhere else. However, now it has been proven that there is considerable overlap in the geographical distribution of both species. Nonetheless, they are identical in their clinical presentation and management (Twarog M, et al, 2015).

Initially, as in the case of *Histoplasma* and *Blastomyces*, *Coccidioides* spp. was classified as a protozoan and named *Coccidioides immitis* (from Latin Coccidia: protozoan and immitis: not mild), an error perpetuated by its dimorphic nature (Gabe ML, et al, 2017). This pathogen was later classified as a dimorphic fungus of the *Onygenaceae* family.

The life cycle of *Coccidioides* includes a pathogenic phase in the host, characterized by a structure called spherule (20-100μ) that originates from the inhalation (rarely by transdermal inoculation) of arthroconidia (3-5μ), the saprobic phase of the fungus; this phase occurs in the environment (and in culture media in the laboratory) in the form of mycelia which, when mature, contain the arthroconidia, which characterizes the environmental phase. These mycelia are fragmented by wind or human activity (e.g. agriculture, archeology, etc.) and are inhaled by the host into the lungs, where they are transformed into spherules completing the life cycle. When spherules mature, they develop endospores (2-4μ) that progressively increase the pressure inside the spherule until they cause the wall to rupture, spreading in neighboring tissues, where each endospore, when mature, becomes a spherule and the cycle is repeated indefinitely until it is stopped either by the host's immune response and/or antifungal treatment. If the spherules are expelled from the host and are deposited in viable soil, they quickly transform into arthroconidia, the infectious form of *Coccidioides*. Most ascomycete fungi are strictly saprobes, but *Coccidioides* spp. has developed the ability to infect mammals, including humans (Laniado-Labor ń et al, 2012).

Both *Coccidioides* species develop in the arid to semi-arid alkaline soils of the western United States, northern Mexico and some isolated regions of central and South America. Most of the *Coccidioides* isolates have recovered between 10 and 30 cm. below the ground surface (Fisher FS et al, 2007). It has been speculated that *Coccidioides* respond to moisture in the soil; after seasonal rains, the fungus develops mycelia and when the soil dries out or the nutrients are depleted, the fungus reproduces asexually disarticulating the hyphae as arthroconidia. These are transported by air and can be inhaled by a host (the hypothesis known as "grow and blow"). It has been reported that in the state of Arizona the seasons with low rainfall correlate well with a higher incidence of primary coccidioidomycosis (Hector RF et al, 2011 & Tamerius JD et al, 2011).

### *1.2 Epidemiology*

The incidence of coccidioidomycosis (CM) reported in the United States has increased markedly in the last 20 years. It constitutes a major public health problem due to the existing challenges for the diagnosis and treatment of this disease. This increase in the number of cases is multifactorial. For example, in Arizona, there has been a 75% increase in population density between 1990 and 2010, partly due to migration, with subjects most likely never exposed to *Coccidioides* and no immune memory for CM. Likewise, with this population growth, the development of suburban areas of desert in the metropolitan areas of Tucson and Phoenix has been necessary, with the consequent removal of the soil and the increase in exposure to dust in the air (McCotter OZ et al, 2019). The hyperendemic areas in the United States are located in the Central Valley of California and in the southern region of Arizona; More than 95% of cases in this country occur in these two states. Approximately 1-2% of cases originate in the states of Nevada, New Mexico, and Utah (Cooksey GS et al, 2016).

Outbreaks of CM have been reported in locations distant from endemic areas, in groups that traveled to these areas, even briefly (Cairns L et al, 2000), as well as reactivation in immunocompromised subjects months or years after having traveled to an endemic region (D'avino A et al, 2012). It has been shown that arthroconidia can be viable for at least six months, and transmission through fomites containing dust from the endemic region has been described (Stagliano D et al, 2007).

CM is the most prevalent deep mycosis in Mexico, and infection rates (assessed by coccidioidin skin test surveys) are similar to those reported in the United States of America (Ajello L, 1967). The states of Baja California, Sonora, Coahuila, and Nuevo Leon report the highest rates of infection by *Coccidioides* spp. in Mexico. These endemic regions are also characterized by a dry climate, alkaline soil, and summers with temperatures up to 50 ℃ with very low annual rainfall. All these factors, as mentioned, favor the presence of *Coccidioides* spp. and its subsequent dissemination through air currents (Laniado-Labor ń R, 2006 & Laniado-Laborin et al, 2019). The most prevalent species in Mexico is *C. posadasii* (Bialek B et al, 2004), while *C. immitis* has also been isolated in the northwest of the country. The burden of disease in Mexico is currently unknown (Casta ñon-Olivares LR et al, 2004). CM was a disease of mandatory reporting in Mexico until 1994, with an average of 1,500 cases reported per year (Baptista-Rosas RC et al, 2007).

The epidemiological information of the CM in Central America is very scarce. Indigenous human cases have been reported in Guatemala and Honduras (Castro A et al, 1951 & P érez-Guisasola E et al, 1960 & Garcia VA et al, 1960). Cases are reported sporadically in Honduras, while in Guatemala an average of six cases per year is reported, mostly in patients co-infected with HIV. In accordance with cutaneous coccidioidin surveys, more cases in the region would be expected, but the lack of knowledge about the disease and of laboratories with limited diagnostic capacity for fungal diseases contribute to these low diagnostic rates. The predominant species in Guatemala is *C. posadasii*, although *C. immitis* has also been isolated in the region (Engelthaler DM et al, 2016).

The incidence of CM in South America is unknown for several reasons: it is not a mandatory reporting disease, there is ignorance about the disease and it is mistakenly diagnosed as tuberculosis, which is also endemic and more frequent than CM. As in other regions, CM in South America occurs in semi-arid areas with alkaline soil, low rainfall, and extreme temperatures. Cases have been reported in Colombia, Venezuela, Brazil, Paraguay, Bolivia, and Argentina (Laniado-Laborin et al, 2019).

*1.3 Risk Factors*

Once inhaled, *Coccidioides* arthroconidia are highly virulent and only one spore is needed to cause disease in experimental animals. Coccidioides is so highly infectious when it is aerosolized that in the past it has been considered as a potential bioterrorism agent and represents a serious risk for laboratory personnel who are not adequately trained to take the necessary precautions in the processing of this fungus (Thompson GR 3 III, 2011).

Although anyone who becomes infected can develop the disease, there are some risk factors for the development of severe forms of CM. It has been described that African Americans, Filipinos (Louie L et al, 1999), pregnant women and patients with immunocompromise of any kind are at greater risk of disseminated disease (Odio CD et al, 2017).

In the United States, the frequency of CM has been increasing progressively in the major age groups; The highest rate of CM in the United States is reported in subjects over 70 years of age with 209 cases for $10^5$ habitants, while the rate in the group of 1 to 4 years is only 7.7 per $10^5$ habitants (McCotter OZ et al, 2019).

Certain occupational exposures such as construction work, agriculture or archeology have been associated with a greater risk of exposure and disease (Freedman M et al, 2018 & Kollath DR, 2019).

Coccidioidomycosis has long been recognized as an opportunistic infection in patients with HIV. As with other opportunistic diseases in HIV, the CD4 count seems to be the most important predictor for disease acquisition and dissemination (Ampel NM et al, 1993). Fortunately, the advent of high-efficiency antiretroviral therapy has achieved a significant reduction in the incidence of CM in HIV-positive patients (Masannat FY et al, 2010).

Diabetes is an important risk factor in Mexico since the country has one of the highest rates of diabetes worldwide (9-4% of the general population suffers from diabetes) and severe forms of CM in diabetics have been reported for more than 30 years (Forsbach-S ánchez GB et al, 1985 & Santelli AC et al, 2006).

Pregnancy confers a special risk, for infection and active disseminated disease. The risk increases when the infection is acquired in the late stages of pregnancy and may be due to changes in sex hormones and decreased cell-mediated immunity (Drutz DJ et al, 1981).

Patients with inflammatory arthropathies are at high risk when receiving immunosuppressive medications, especially biologics (Bergstrom L et al, 2004 & Mertz LE et al, 2007); likewise, patients with hematologic malignancies have an increased risk of dissemination (up to 20%) associated with high mortality (50%) (Blair JE et al, 2005).

Coccidioidomycosis is the most common of the endemic mycoses in solid organ transplant recipients in the United States of America (Logan JL et al, 2001). Coccidioidomycosis rates in transplanted patients in the 1970s to 1980s reached approximately 9%, with disseminated disease in up to 75% of the cases and more than 60% mortality. These figures have decreased thanks to antifungal prophylaxis in selected high-risk patients (Blair JE, 2007).

*1.4 CM Clinical Features*

Approximately 60% of individuals who are exposed to *Coccidioides* spp. develop an asymptomatic and self-limited infection, which confers immunity in the future and can only be detected by a skin test or serology.

The remaining 40% of infected subjects develop a condition known as primary CM, Valley fever or Desert Rheumatism. After exposure, the incubation time before the onset of symptoms is 7 to 28 days (Gabe LM et al, 2017).

Primary CM initially presents with an influenza-like picture with cough and fever in 75% of cases, pleuritic pain/pleural effusion, arthralgia, inflammation of major joints and different types of skin rashes including erythema nodosum and erythema multiforme. These skin manifestations constitute an immunological reaction to fungal antigens and not a manifestation of disseminated disease; in fact, its presence has been associated with a lower probability of disease progression (García-García SC et al, 2015). In most patients, this acute syndrome is self-limited, sometimes leaving pulmonary cavitation as a sequel (Laniado-Laborín R, 2006).

Primary pulmonary coccidioidomycosis usually presents as lobar or segmental pneumonia. The radiography usually shows in addition to parenchymal opacity, unlike bacterial pneumonia, hilar or mediastinal adenopathy. In some endemic regions, up to 30% of pneumonia acquired in the community is due to CM (Sunenshine RH et al 2007). Unfortunately, even in endemic regions, clinicians do not request a sputum or serology test to rule out CM in cases of community-acquired pneumonia (Chang DC et al, 2008).

As the infection progresses to resolution, the most common pulmonary sequelae are a residual pulmonary nodule (coccidioidoma) or a thin-walled cavity with no pericavitary reaction (Farness sign) (Madrid GS, 1974). In the case of coccidioidoma, depending on the age of the patient and the presence of risk factors, the differential diagnosis with a neoplasm will have to be established.

Primary CM can evolve into chronic fibrocavitary pneumonia, a more common complication in diabetics, that manifests clinically with chronic constitutional and respiratory symptoms, including weight loss, fever, nocturnal diaphoresis, cough and sputum production (Twarog M et al, 2015). Cavitations can be complicated by the presence of an intracavitary mycetoma, usually by *Aspergillus* spp. (Rohatgi PK et al, 1984).

It is estimated that pleural effusion complicates 5% to 15% of cases of primary pulmonary CM. The examination of the liquid obtained by thoracentesis generally demonstrates an exudate with high protein and lactic dehydrogenase (DHL) content; The cell count usually shows a mononuclear predominance and occasionally eosinophilia. Approximately one-fifth of the cases meet the criteria for complicated parapneumonic effusion or an empyema that requires drainage by closed pleurotomy (Merchant M et al, 2008). It is rarely possible to isolate *Coccidioides* spp. from the pleural fluid. In cases that require surgery or pleural space biopsy, the histopathological study demonstrates chronic granulomatous inflammation (Shekhel TA et al, 2014).

Approximately 1% of CM cases will progress to a disseminated form, involving the skin, bones and joints, the central nervous system and other organs and systems.

The skin's involvement by dissemination is commonly manifested as nodules, papules, gums (a chronic inflammatory nodular lesion that softens the tissue affected by necrosis, which eventually expels a thick content), acneiform pustules, warty plaques, and abscesses with fistulas (García-García SC et al, 2015). These lesions usually involve the face, neck, scalp and chest wall. In addition to the presence of the spherules, the histopathological study typically shows necrotizing granulomas. Given the impact of the disseminated disease on the prognosis and management, it is important to distinguish these dermatological manifestations that indicate dissemination, from the dermatological findings of primary CM that are self-limited and do not require specific treatment. The skeletal disease usually manifests itself in the form of a monoarticular (more commonly knee) condition, or vertebral or bone osteomyelitis of the lower extremities.

Central nervous system (CNS) involvement is the most severe form of disseminated CM. It usually develops months after the initial infection, but it can occur years later. Subacute onset is possible, but most cases are chronic, with insidious onset. Up to half of the patients develop obstructive hydrocephalus that requires urgent surgical bypass. Also, up to 50% of patients develop vasculitis with cerebral infarction (Johnson RH et al, 2006 & Mischel PS et al, 1995). Clinical manifestations include persistent headache, nausea, vomiting, and visual disturbances. In patients with a previous diagnosis of CM this is an indication for imaging studies, and if indicated, a lumbar puncture to obtain cerebrospinal fluid (CSF). The CSF shows in these cases mononuclear predominance and occasionally eosinophilia and hypoglycorrhachia. The sensitivity of microbiological tests is very low, including that of culture and diagnosis is based on serology. A complement fixation titer >1: 2 is considered diagnostic.

In endemic regions for both conditions, tuberculosis and CM may coexist. They share epidemiological, clinical, radiographic and histopathological characteristics, which can complicate the diagnosis. It is important to emphasize that the diagnosis of one of them does not exclude the coexistence of the other (Castañeda-Godoy R et al, 2002).

*1.5 Diagnosis*

There are three basic methods for the diagnosis of CM: microscopy, culture, and serology.

The identification of typical spherules of 20-80 μm in sputum smears or body fluids using potassium hydroxide or Papanicolaou stain, or their presence in histopathological specimens (stained with PAS or Gomori´s silver stain) is considered a confirmatory test for CM. The histopathological study shows a granulomatous inflammation process, very similar to that of tuberculosis.

Unlike other endemic fungi, *Coccidioides* spp. It grows rapidly at 35 ℃ in a variety of media. The isolation of *Coccidioides* spp. in culture constitutes the gold standard for diagnosis. The fungus can be isolated in culture from sputum, tissues and body fluids, and its isolation from any site is diagnostic of the disease. *Coccidioides* spp. does not require special culture media, though Sabouraud's medium is preferred when available. It usually grows in 2-7 days, with non-pigmented colonies and the development of septated hyphae that contain arthroconidia. *Coccidioides* spp. constitute a significant biological risk for laboratory personnel. The identification of the fungus can be done through the use of a genetic probe (AccuProbe, Gen-Probe, Inc., San Diego, CA, USA). All specimens of a patient with suspected CM should be processed under level 3 biosecurity conditions (Ampel NM, 2010). Mycelia can sometimes be detected in histopathological sections if tissue conditions simulate that of the environment, especially in diabetic patients, and this can lead to misdiagnosis (Muñoz-Hernández B et al, 2008).

The production of antibodies in CM is delayed by several weeks with respect to clinical manifestations and with an even more delayed and weak response in immunocompromised patients (Blair JE et al, 2006). Therefore it is recommended to perform serological tests to reduce the probability of false negatives. In contrast to other infections, in CM the antibody concentrations generally decrease over time to undetectable levels when the clinical picture is resolved. For this reason, the presence of positive serological tests indicates recent infection, chronic active disease or reactivation (Pappagianis D et al, 1990).

There are several types of serological tests available for the diagnosis of CM. These include the tube precipitin test (TP), the tube complement fixation test (CF), an agar immunodiffusion tests for TP and CF (IDTP and IDCF), the latex agglutination test (LPA; as the TP mainly detects antibodies IgM) and enzyme-linked immunosorbent assays (ELISA tests). These tests are based on the identification of IgM and IgG antibodies to fungal antigens. In the acute phase of the disease up to 50% of patients have detectable IgM antibodies in the first week and up to 90% in the third week. IgM antibodies are negativized after three months. On the contrary, IgG antibodies tend to be positive between the first and third months of evolution. The quantitative results of the CF test are useful to determine the severity and response to treatment: a CF titer of ≥1:16 is considered as indicative of serious disease and/or dissemination (Paris JM et al, 2008). In people recovering from the disease, both reactions usually become negative.

The ELISA method (Premier EIA, Meridian Diagnostics, Inc., Cincinnati, OH, USA) for the detection of IgG and IgM is a qualitative test with high sensitivity (98.5%) and specificity (95.5%) when compared with traditional TP and CF tests and is frequently used for clinical diagnosis. This test is run as a panel for TP and FC maximizing its sensitivity. A positive EIA for IgG, either isolated or together with a positive EIA for IgM, should be sent to a reference laboratory for confirmation. This is usually done by an immunodiffusion CF test. A negative EIA panel does not require confirmation by other types of tests, but it is recommended to repeat it because the initial test could have been carried out before seroconversion (or there can be a late serological response in immunosuppressed patients). The EIA test has a shorter response time and greater sensitivity (but less specificity) when compared with the immunodiffusion test. The IDTP (immunodiffusion tube precipitin) and IDCF (immunodiffusion complement fixation) tests can be performed as initial tests in reference laboratories, or the IDCF can be performed to confirm a positive in an EIA IgG test. When you have an EIA test for CF or a positive IDCF, it is recommended to run the traditional FC test to provide quantitative information about IgG titles. High titles (≥1:16), as mentioned, suggest dissemination. It is important to mention, however, that there are exceptions where patients with disseminated disease have titers <1:16 and patients without the disseminated disease have titers ≥1:16 (Crum NF et al, 2004). CF titles are followed serially to assess the response to treatment.

An alternative strategy is the detection of fungal antigens in the serum by an ELISA test. An example of this type of test is the detection of the galactomannan antigen of *Coccidioides* spp. (MiraVista Diagnostics, Indianapolis, Indiana), although there are reports of cross-reactions with histoplasmosis and blastomycosis. Antigenemia can be detected in more than 70% of immunocompromised subjects with severe or disseminated disease, a population in which serological tests are less reliable (de Aguiar-Cordeiro R et al, 2013 & Durkin M et al, 2008).

There are commercial tests, based on real-time PCR. The identification of *C. immitis* and *C. posadasii* is based on the sequencing of the fungal rDNA.

Skin tests using coccidiodin or spherulin as an antigen historically played a vital role in the epidemiological investigation

of CM (Laniado-Labor ń R et al, 1991). These tests are a typical example for the detection of cellular or late immunity, and only indicate that the subject has been infected by *Coccidioides* spp; they are not useful to establish the diagnosis of active disease (Gabe LM et al, 2017).

*1.6 Treatment of CM*

Since the 1930s, it is known that most cases of CM are self-limited and resolve without treatment. Although it is well established that severe forms of the disease require treatment, it is not yet defined which patients with primary CM would benefit from receiving treatment for the purpose of accelerating recovery and preventing dissemination. It is important, however, to mention that many of the current recommendations are based on expert opinion and not good quality evidence.

The first effective drug for the treatment of CM was amphotericin-B (Laniado-Labor ń et al, 2009), but due to the need to administer it intravenously and its significant toxicity (especially renal toxicity) has been almost completely replaced by azoles (itraconazole, fluconazole, voriconazole, posaconazole e isavuconazole).

Fluconazole (90%), voriconazole (96%) and isavuconazole (98%) have excellent bioavailability after oral administration, while itraconazole (55%) and posaconazole (54%) have much lower bioavailability (Thompson III GR et al, 2019).

An exception for the use of azoles is pregnancy during the first trimester due to teratogenicity; in these cases, the use of amphotericin B is required (the lipid formulation is preferred), and constitutes the drug of choice in this population (Thompson III GR et al, 2019). Azoles can replace amphotericin B after the first trimester to avoid prolonged intravenous therapy and its toxicity (Bercovitch RS et al, 2011).

Fluconazole is the drug preferred for the treatment of meningeal disease due to its better penetration (60%) in the cerebrospinal fluid. The dose may vary from 400 to 800 mg, but doses as high as 2,000 mg (Johnson RH et al, 2006) have been used; itraconazole and posaconazole do not penetrate the CSF, while the penetration of voriconazole into the CSF is only 50%.

Primary lung disease often does not require antifungal therapy. Some experts recommend the treatment of primary lung disease in African American or Filipino patients, given the higher frequency of more severe forms in these ethnic groups. Other situations in which experts recommend treatment are patients with extensive pneumonia and prominent hilar adenopathy (Galgiani JN et al, 2000).

Pulmonary nodules constitute a sequel to the primary CM and do not require treatment, although it is necessary to establish the differential diagnosis with pulmonary nodules of malignant origin. Pulmonary cavitations are also a sequel to primary CM and are usually asymptomatic and managed only with clinical observation. Occasionally they present with cough or hemoptysis; in case of recurrent bleeding or severe (uncommon) hemoptysis, they may require surgical removal. Another indication of surgery is a bronchopleural fistula with pneumothorax and empyema (Ashfaq A et al, 2014). Chronic CM pneumonia requires azole therapy for at least one year (Ampel NM, 2015).

Regardless of whether or not primary CM has received treatment, patients should be followed in their evolution with serial titers of complement-fixing antibodies and imaging. Current clinical guidelines recommend administering treatment in cases of primary CM in immunosuppressed patients, those with significant comorbidities and patients with CF titers ≥1: 32 (Galgiani JN et al 2016).

The duration of therapy varies according to the site and severity of the disease. Primary lung disease, if treated, usually requires treatment for less than six months.

All cases with dissemination require therapy. As in cases of very severe lung disease, patients with severe disseminated disease are initially treated with amphotericin, while less severe cases are treated with oral azoles. The duration of therapy is at least 1 year. Meningeal CM, on the other hand, requires lifelong treatment given the high recurrence rate when treatment is stopped (Blair JE, 2009).

Neither amphotericin-B nor the azoles are fungicidal vs. *Coccidioides*, emphasizing the need for an efficient cellular immune response. The pharmacological treatment of CM in patients with HIV should not underestimate the importance of antiretroviral treatment (Li Rk et al, 2000).

A well-known fact is that patients recovering from CM have prolonged immunity to reinfection. This would suggest an important role for a vaccine (Pappagianis D, 2001); however, despite the extensive work done in this area, there is no effective vaccine for clinical use to date.

**2. Atmospheric Science and Coccidioidomycosis Risk Avoidance**

Inhalation of the soil-dwelling mold spore, *Coccidioides* arthroconidia (segments 3-5 μ in length) costs and consequences for California are reported in Wilson, et al. (2019); a similar assessment is underway for Arizona which, combined with

the California data, will cover nearly 90% of all CM cases in the United States (Galgiani, 2020).

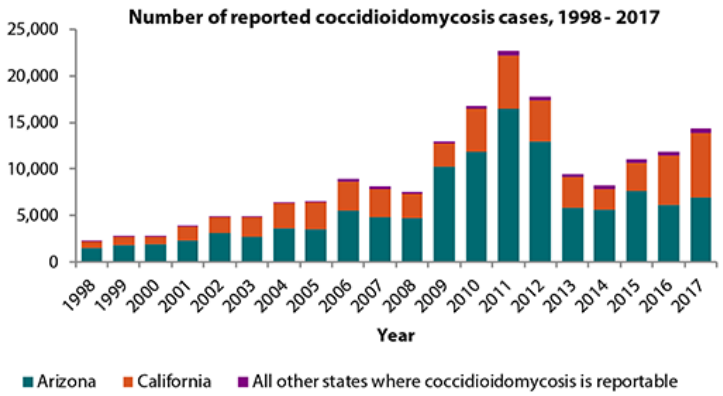
Several mid-20th Century studies (e.g. Egeberg and Ely, 1956; Plunkett and Swatek, 1957; Maddy, 1965, 1957) postulated links between Valley fever and weather conditions (primarily rain and temperature). Smith, et al. (1946) and Maddy (1965) speculated that wind could distribute the fungus further to expand areas of contagion.

A 1977 Kern County, California dust storm provided a first convincing, fact-based argument that Valley fever could be spread by its fungal spore arthroconidia (*Coccidioides immitis*) transported by winds from distant locations (Pappagianis and Einstein, 1978). Seventeen years later, Stevens (1995) reported that viable Cocci arthroconidia could, indeed, be carried by the wind. And three years after that, Schneider, et al. (1997) attributed an outbreak of Valley fever in Ventura County, California, to aerosolization and transport of cocci spores some 40 km from the Northridge earthquake of 17 January 1994.

Understanding the atmosphere's role in risk for Valley fever is a matter of research. Application of that understanding is a matter of policy. But research has been slow to respond to the obvious clues strewn along the path toward applicable science.

Most incentive for research support is retrospective. Research priority is hard won. It is decided in uphill scrimmage, especially without a well-documented cause for concern, e.g. a substantial economic or health consequence, or if tools and data are unavailable. Other restraints include perceptions of being locally or regionally confined, or if the problem is described as theoretical or anticipated.

The US Centers for Disease Control and Prevention attribute, on average between 1990–2008, 200 deaths per year to Valley fever across the United States (CDC, 2018). The following graph from the CDC shows the number of reported US cases between 1998 and 2017.




Reasons for large interannual deviations from the norm have included changes in the population at risk, construction that disturbs the soil, and variance in diagnostics or reporting. A change in rainfall (where, when and amount) is a common prime suspect and cohort (Cooksey, et al., 2017; Bezold, et al., 2016).

But what if the bounds of CM endemicity change because precipitation or wind patterns change in tandem with global shifts in climate? The subject was raised in the first Congressionally mandated National Climate Assessment of the Potential Consequences of Climate Variability and Change (Sprigg and Hinkley, 2000). Cocci spore ranges have grown. They are projected to expand and infect well beyond current boundaries. Tong, et al., (2017) connect increased intensity of dust storm activity and Valley fever infection in the southwestern United States. Goris, et al. (2019) extrapolate current US Cocci endemicity northward and further east, more than doubling the area affected by the end of this Century; their study included growth in human population (Hauer, 2019) and used temperature and rain distributions projected by the Coupled Model Inter-comparison Project used for the Intergovernmental Panel on Climate Change 5th Assessment Report (Stocker et al., 2013).

Rigorous statistical analysis of atmospheric pressure, temperature, precipitation and wind, show that climate variability explains less than 5% of Valley fever incidence (Zender, Talamantes and Behseta, 2007). This analysis revealed an important detail, that infection correlated well with the previous year's precipitation (i.e. a nine-month lag)—evidence that confirmed the Kolivras and Comrie (2003) scenario of successive regimes of moisture, heat and aridity that could lead to high numbers of CM cases. Comrie (2005) found that summer precipitation and current $PM_{10}$ explains up to 80% of CM incidence between1992–2003.

Other studies confirmed and detailed the climate-cocci link by mid-decade and after (see, e.g. Comrie, 2005; Zender and Talamantes, 2006; Talamantes, Behseta, and Zender, 2007; Comrie and Gleick, 2007; Crimmins, et al., 2016; Weaver and Talamantes, 2018.) Optimum conditions include a wet season for the fungus (*coccidioides*) to grow in the soil, followed by a long, hot, dry period to make the fungus brittle, broken and ready for a gardener's shovel, a farmer's plow, a coyote's dig to make the spore airborne and available to inhale and infect.

This conversation between atmosphere and health scientists encouraged mycologists and soil scientists to join the discussion. Their first collective opportunity returned to climatic conditions for growth, desiccation and aerosolization of the *Coccidioides* spore, and explored potential to forecast downwind infection risk. Science, service and policy of environmental health for Valley fever finally came together in a 2012 workshop in Tucson, Arizona, sponsored by the U.S. Centers for Disease Control and Prevention (CDC) and NASA. (Fisher, et al., 2012; Sprigg, 2012). Nearly a decade of NASA's Applied Sciences Division research—PHAiRS (Public Health Applications in Remote Sensing; 2004-2009) and ENPHASYS (Environmental Public Health Application Systems; 2009-2012), directed through the University of New Mexico and the University of Arizona—had to this point (EDAC, 2011; Morain, 2011).

Opportunity to reduce risks for Valley fever, asthma and other respiratory and cardiovascular disease could be seen and tracked early in a NASA project, Public Health Applications in Remote Sensing (PHAiRS). Researchers recognized that health risks, including those of CM, might be mitigated if recent advances in satellite observing systems and numerical models were applied to simulate and forecast desert dust emissions and downwind dispersal (see, e.g., Sprigg, 2008).

Airborne mineral dust priority rose substantially with concerns of the Intergovernmental Panel on Climate Change (IPCC and Houghton, 1990; IPCC, 1995; IPCC, 2001; IPCC, 2007; IPCC, 2014). Albeit not because of potential health issues. More to the IPCC's point, Earth's radiation budget and climate are affected by airborne particulates.

Yet, as late as 2018 the IPCC shows no apparent alarm for potential health risks from airborne mineral dusts (IPCC, 2018; Hoegh-Guldberg, 2018). Yet, changes in climatic patterns of precipitation or temperature may expand or contract arid lands, their particulate emissions, and the growth and extent of *C. immitis* or *C. posadasii* spores and their aerosolized emissions. The IPCC fails to mention Valley fever or coccidioidomycosis. But, the fourth in the series of aforementioned Congressionally mandated National climate assessments does continue vigilance regarding CM and climate variability and change (Ebi, 2018).

As to tools and data, the sciences of medicine and epidemiology began to accumulate international evidence of respiratory and cardiovascular harm of airborne mineral (i.e. aeolian) dusts (UNEP, WMO, UNCCD, 2016) and US-centric interests in CM brought attention to the variety and incompatibility of methods by which the disease was diagnosed and reported. This was resolved in 1995. With that understanding, priority to investigate rose because technology and data to meet it had advanced.

Computer speed and capacity has grown. By 2000, first steps had been taken to handle vast quantities of data more economically (Foote, 2017)), which meant that goals in forecasting airborne dust could be set higher: 3-D dust concentration forecasts in shorter time steps with high spatial resolution (3 km) over larger areas. New satellite sensors, systems (e.g. NASA's 'A-TRAIN', see NASA, 2020) and international collaborations (see NASA, 2016; NOAA, 2020) offered means to detect, dissemble and monitor airborne particulates over the globe—and to detect and monitor their sources at spatial resolutions of meters and time resolution of days.

Numerical weather forecast models have also improved: useful forecast accuracy grew from three days in the 1980's to five days at the turn of the Century (Wallace and Hobbs, 2006). Ever sharper spatial resolution remained high priority in atmospheric dust model development. By 2014, the NMME/DREAM (Non-hydrostatic Mesoscale Model, E-grid, Dust Regional Atmospheric Model) developed and applied for the American Southwest during PHAiRS, ENPHASIS and the CDC Valley fever project (Morain and Sprigg, 2005; 2011; Sprigg, 2012; Sprigg, et al., 2014) had improved to 3.5 km (Vukovic, et al., 2014). Cocci detail lagged, and still does, except for a few bursts of enhanced surveillance, encouraged by success in disease syndromic surveillance in general (e.g. Katz, et al., 2011).

However, to the consternation of Demosthenes Pappagianis (Personal communication, 2010), collaboration between atmospheric and CM health science was slow and incomplete. Valley fever is not a reportable disease in Texas https://ci.lubbock.tx.us/departments/health-department/disease-surveillance (accessed 01/20/2020), and not a concern for the PHAiRS project in 2005 (Morain and Sprigg, 2005) when the disease could have been included along with asthma in a stakeholder partnership with the city of Lubbock, Texas. Yet, by 2004, newspaper reports, albeit unalarming, called attention to CM in the Lubbock region (Baker, 2004). Atmospheric model forecasts or simulations had not yet been considered for CM risk reduction even as late as 2011 (Morain and Sprigg, 2011) when another public health stakeholder—New Mexico public school nurses and the State health department—considered asthma but not Cocci risk abatement. At least one inhibiting factor would have been responsible in both cases: surveillance for Cocci and model spatial resolutions were not yet compatible.

To avoid risk of exposure to C. immitis or C. posadasii an understanding of their relationship to climate is but a small, albeit significant, step. Advance notice of imminent risk, warnings of an approaching spore-laden dust cloud, for example, would lower risk of contagion greatly. To get there, the conversation within atmosphere, soil, plant and health science and service must turn into collaboration. The sought-after parts of collaboration are evident, largely ongoing but separate. Where they are not joined, a bit of connective policy and priority will suffice.

We learn from an example of interdisciplinary science and policy collaboration. Countries along southern reaches of the Sahara Desert, the African Sahel (Mali, Niger, Chad and Sudan), have faced periodic annual outbreaks of Meningitis for many years (Spiegel et al., 1994; Nicolas, Chippaux, and Martet, 1996), enough so that the region became known as the "meningitis belt." Research suggested a meteorological trigger: aeolian Saharan dust episodes (e.g. Lapeysonnie, 1963; Cheesbrough, Morse and Green, 1995), which became fairly well established by 2014 (see Pérez García-Pando, et al., 2014)—Pappagianis would be pleased by the long and close research collaboration of medicine, epidemiology, meteorology, climatology and aeolian dust modeling. Yet, even in 2010, the potential role of windblown dust in Valley fever had been low priority within the medical research community (Mueller and Gessner, 2010) /1/.

## 3. Coccidioidomycosis: A Spatio-Temporal Perspective

Coccidioidomycosis (CM) is a disease of major public health importance due to the challenges in its diagnosis and treatment. To understand CM requires the attributes of a multidisciplinary network analysis to appreciate the complexity of the medical, the environmental and the social issues involved: public health, public policy, geology, atmospheric science, agronomy, social sciences and finally humanities, all of which provide insight into this population transformation (Smith, 1940; Fiese, 1958; Hirschmann, 2007; CDC, 2001; Galgiani, 2005 & 2008); Pappagianis and Einstein, 1978; Sprigg et al., 2008 & 2012 & 2014; Sarafoglou and Kafatos, 2013; Sarafoglou et al., 2019; IPCC, 2007; Hospenthal, 2013; Gia, 2014; and Deresinski and Mirels, 2019).

In section 2 of this paper, we highlight the most important contributions and controversies in the history of the CM-research by using scientometric or bibliometric research evaluations that are based on Garfield's work (Garfield.library.upenn.edu) on the propagation of scientific thinking. (Garfield initiated the old "Science Citation Index", the forerunner of the modern equivalent "Web of Science" database).

The study of CM is multi-disciplinary, with scientific and humanitarian concerns. Yet, poor communication both between and within disciplines is a recognized challenge today.

There are many scientometric or bibliometric databases, e.g. Google Scholar, PubMed/Medline, CrossRef, Web of Science, etc. Our bibliometric analysis of CM-research is based on Web of Science (WoS) database for the period 1938-2017 /2/. Our sample consists of 2,188 items.

WoS has two advantages:

1. It has a long data period.
2. It has a better classification system than the other databases e.g. Google Scholar.

### *3.1 The Spatio-Temporal Distribution of the CM-Research*

The first 80 publications years of CM research by record count are shown in Figure 1.

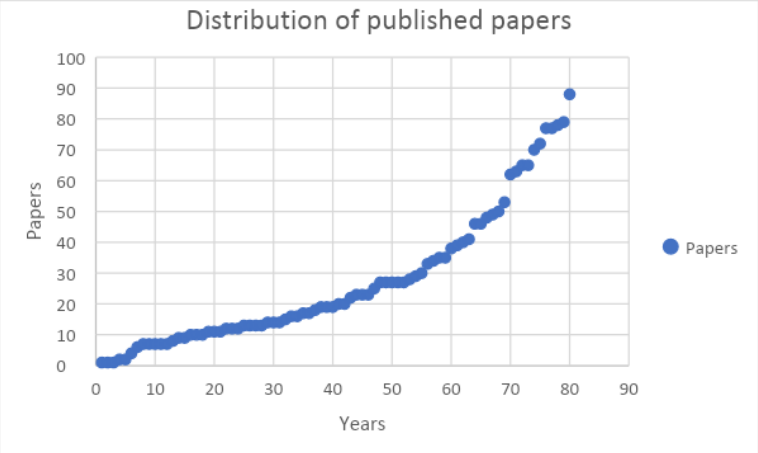



Figure 1. The first 80 publications years of CM research by record count

In Figure 1, the significant increase in published works during this period can be observed. There are two important evolutions for scientific creativity during this long period 1938-2017:

1. Garfield's scientometric or bibliometric evaluations of research. Merton (1968), de Sola Price (1976) and Zuckerman (1987) extended Garfield's ideas with the "Matthew effect" and the complex problem of intellectual influence.
2. The diffusion of the Internet changed the accessibility of scientific publications. The accessibility of scientific publications is more efficient in the last years (Sarafoglou, et al., 2012).

According to the Web of Science data during the first period of CM- research, namely 1938-1978, the publication rate was low. The eponymous publications of the first period generated sufficient dynamics for new citations in the next forty years.

An interesting observation is a CM-research distribution between geographical areas and countries. One should expect North America, Central America, and South America are the most prolific areas, because of the spatial configuration of CM.

Highly endemic areas for coccidioidomycosis include California's San Joaquin Valley, and south and east along a broad swath of territory along both sides of the US-Mexico border, through Central America and deep into South America (Laniado-Laborin, 2007). Overall, even today throughout the endemic region, cocci surveillance is poor. Yet, some statistics give us an idea of the seriousness of the disease. On average, 150,000 people in the U.S. are estimated to contract valley fever annually where, between 1990 and 2008, an annual average of 161 deaths were attributed to CM. Most of these cases are unreported because initial symptoms are not severe and normal resistance prevails over time. Most documented cases come from the U.S. state of Arizona where, in 2007, approximately 3000 cases were reported (there were 6000 cases reported nation-wide), with an associated 1735 hospital visits and $86 million in hospital charges (ADHS, 2007; ADHS, 2012).

In California, Pappagianis (1994) documented increases in CM cases from 1991 to 1993, Huang, (2012) and Sondermeyer, et al., (2013) found an average of 70 deaths each year from CM between 1997 and 2008. Medical records for Kern County, California, attribute approximately $45 million in direct costs for hospitalization and outpatient care for CM-cases during the period 1991–1993 (CDC, 1994). And, Kern County shares much of the San Joaquin Valley.

Physicians in the US required to report a diagnosed case of CM after 1997. Also, methods of laboratory blood tests for cocci have changed over time, and the time-dependent record of surveillance for CM is poor (Sprigg, et.al., 2014).

In the next Table 1 we may note the actual research distribution of countries by record count.

Table 1. The most prolific countries in the CM-research

| |
|---|
| USA (1,482) |
| Mexico (68) |
| Brazil (58) |
| Germany (32) |
| Canada (27) |
| France (25) |
| Argentina (24) |
| England (20) |
| Japan (14) |
| Italy (14) |

The USA is the dominant country in the publication of CM-research. Mexico and Brazil are the most prolific countries with Spanish or Portuguese language.

English is the modern "Franca lingua" for scientific production (Sandelin and Sarafoglou, 2004). The quantity and the quality of the American Universities could be a major explanation too.

It turns out that there is a tendency for a higher publication rate for English-language countries, slightly lower for countries with the less commonly spoken languages, and even smaller for countries with large non-English languages.

This is consistent with the hypotheses that there is a bias in the databases from the ISI such that English-language journals tend to be overrepresented, that scholars from English-language countries write almost exclusively in English, and that scholars from other countries tend to publish less in English and more in their domestic language the larger their domestic language. This calls for caution in using these databases for international comparisons of research activity.

One of the outliers in Table 2 is Germany. Germany is not connected geographically with the CM-regions, but Germany has produced more publications than endemic countries, e.g. Argentina.

The explanation might be the educational background of the Argentinian student Alejandro Posadas. He was the first author of CM-research. He wrote, "*Un nuevo caso de micosis fungoide con psorospermias*" (1892). Posadas studied in Buenos Aires, and his professor Roberto Wernicke was another Argentinian with German parents. Wernicke studied at Jena University in Germany, and he became a professor in Buenos Aires after his return to Argentina.

He published an article (1892) after Posadas' publication for CM with the title "*Über einen Protozoen befund bi Mykosis Fungoides*". This article generated a new scientific research in Germany (Sarafoglou, et al., 2012).

There are two other prominent CM-researchers who studied or were born in Germany:

1. William Ophüls

   William was born in Brooklyn, but he went to study in Germany. He returned to US after his studies at Würzburg and Göttingen, and he became a professor in California some years later.

2. Hans E. Einstein

   Einstein was born in Berlin and he emigrated from Germany to the USA via Holland during Hitler's early period at age 16. He was an Albert Einstein's relative. He got a medical degree from New York Medical College. He was active in California too.

The first North American CM-article was published by Emmett Rixford and TC Gilchrist (1986). Fiese (1958) wrote that this paper "was the first extensive study of CM and the first in which the significance of the parasite, as the agent of the new and disease, was appreciated."

But Table 1 is a manifestation of international cooperation and the migration of researchers.

*3.2 The Publications*

Another interesting question is the distribution of Science Categories of the CM-research.

In the next Table 2 this distribution is depicted:

Table 2. The distribution of Science Categories and Source Titles of the CM-research

Infectious Diseases (515)

Medicine General Internal (349)

Immunology (349)

Microbiology (328)

Mycology (229)

We can observe that the category Infectious Diseases is the most dominant Science Category. In order to understand better the distribution of Science Categories of CM-research, we may look at the distribution of Source Titles:

Table 3. The distribution of Source Titles of the CM-research

Clinical Infectious Diseases (105)

Infection and Immunity (56)

American Review of Respiratory Disease (50)

Mycopathologia (42)

Chest (41)

A journal for "clinical infectious diseases" has published most of the CM-articles.

There is an overlapping between Table 2 and Table 3:

Namely, the terms “infectious diseases” and “mycology” are common in both Tables.

**4. The Significant Authors, Editors and Organizations.**

Our database can provide information to estimate the most prolific authors and the most citated authors of the CM-research.

The most prolific authors are in order in Table 4:

Table 4. Prolific Authors in Terms of Publications

| |
|---|
| Pappagianis D (94) |
| Galgiani JN (89) |
| Stevens DA (84) |
| Ampel NM (77) |
| Blair JE (63) |

Charles Smith’s epigone Demosthenes Pappagianis has been studied at Stanford and Berkeley and now works at UC-Davis. He is one of the oldest and the most productive CM-researchers in the world (90+ years old).

John Galgiani and Neil Ampel work at the University of Arizona.

Editors are also important in the scientific diffusion of the CM-research. In Table 5 the most important editors are evaluated:

Table 5. Editors

| |
|---|
| Einstein HE (39) |
| Clemons KV (37) |
| Stevens DA (36) |
| Laniado-Laborin R (36) |

It seems that the four most important editors have almost equal production.

The next Table 6 depicts the organizations with the number of publications.

Table 6. Organizations

| |
|---|
| University of California System (369) |
| University of Arizona (244) |
| University of California-Davis (138) |
| Mayo Clinic (106) |
| Stanford University (100) |

The two CM-infected states in the US are also the most productive in research: California and Arizona.

Stanford and UC-Berkeley have a historical value-added of research per se within the California state.

Davis was once the agricultural college of Berkeley. However, when Davis became independent of Berkeley, a group of CM-scholars (Pappagianis and others) moved from Berkeley to Davis with their laboratory.

This is the explanation of the high productivity of UC-Davis.

The citation is an index of research impact. The most cited authors of the CM-research are written in Table 7.

Table 7. Citations

| | |
|---|---|
| Wallis RS et al. (2004) | ..531 |
| McNeil MM et al. (1998) | ...432 |
| ..... | |
| Galgiani JN et al. (2005) | 287 |
| Zwirewich, CV et al. (1991) | ..261 |
| Drutz DJ (1978) | ..257 |

The first two articles are Conference Articles, and the other articles are Journal Articles. The citation is an index of the research impact. Galgiani is one of the most prolific and cited authors. He might verify the "Matthew effect" in the CM-research (Merton, 1968):

"A macroscopical version of the Matthew principle is apparently involved in those processes of social selection that currently lead to the concentration of scientific resources and talent. "

**5. The Financing of CM-research.**

Finally, the financing of CM-research is a vital and complex question which affects the entire subject area. There are major differences between regions: North America vs. Latin America, America vs. Europe, Germany vs. other EU-states, etc.

The medical control system of a country to produce a new medicine is extremely important too. The form of longitudinal studies (number of patients and the number of years) can increase the costs of the new medicine.

Yet, research shows that a vaccine is, indeed, possible (Cole, et al., 2004; Galgiani, 2008) and perhaps a change in the conventional business model for vaccine development should be modified, as Galgiani suggests.

> "The industry had been slow to invest, with prior outbreaks limited in
>
> scale and a virus believed confined within poor countries."

We may expect that the Funding Agencies based in the US will be the dominant agencies in the international market.

Table 8. Funding Agencies

| |
|---|
| NIAID NIH HHS (84) |
| Pfizer (16) |
| NIH (9) |
| Astellas (9) |
| Merck (8) |

The National Institutes of Health (NIH) finance more CM-projects than the private companies. There is no available information in our sample for the money value of these projects.

It may take an international partnership between industry and governments to solve or significantly reduce the problem of CM, mutually investing in risk avoidance measures, to "promote the general welfare," a purpose of government, as the preamble to the U.S. Constitution states. Long-term views are needed, a higher quality of government, as important questions arise because the cocci fungus is so linked to the variability of weather and future climates – and to how society responds (Sarafoglou et al., 2016). Will deserts and the range of CM expand or "migrate" to unsuspecting populations? Employment in solar energy fields has become a new, high-risk occupation for CM in this growing industry. Will new industry or agricultural "migrant" workers from non-endemic areas be especially vulnerable?

Recently, Deresinski and Mirels, (2019) wrote:

"The search for the "Holy Grail" - a vaccine capable of preventing this disease-continues".

**Epilogue**

Coccidioidomycosis research is multi-disciplinary, on a path toward inter-disciplinary or trans-disciplinary. Mycology, Geology, Atmospheric Science, Medicine, Epidemiology and Public Health are chief disciplines. Greater interaction of

these disciplines could generate more effective CM-treatment. The complexity of CM research needs an holistic (transdisciplinary) approach.

Epidemiological evidence for weather-influences on Valley fever is reasonably documented. But climate variability or change is a looming concern, and the scrimmage for priority has begun. Will spatial and temporal patterns of CM be altered because climate wanders off its path of recent centuries? Reason argues that CM cases that are diagnosed further north should be explained, especially as public awareness grows (Santoro, 2019). Gorris, et al., (2019) estimate that by 2100 under a high warming scenario sketched by the Intergovernmental Panel on Climate Change (IPCC), the U.S. area of climate-limited CM endemicity will more than double, the number of U.S. States affected will increase from 12 to 17, and the number of Valley fever cases will grow by 50%.

Societies have gradually integrated what is known about CM and its favorable and unfavorable environmental conditions to establish public health policy. Will these policies be obsolete, outdated by new climatic norms?

Meteorologists begin to define atmospheric processes as "climate" when predictions of "weather" appear no longer possible: about two weeks into the future. A forecaster may attempt to foresee the chance of rain on your holiday parade two weeks from today, but the inaccuracies of weather observations and the chaotic nature of the atmosphere make it unlikely—a reminder of Robert Browning's /3/, *"... a man's [sic] reach should exceed [his] grasp, or what's a heaven for?"* These same limitations apply to future forecasts and warnings of CM risk.

As we have seen, variability in the climates of wind, temperature, sunshine and precipitation are built upon patterns of weather. And weather, we have found from mycology, geology and epidemiology, affects the growth, spread and emergence of CM—albeit in complicated and still investigated ways. These "ways" will drive future research to lower the risk of CM infection, which will include the micrometeorology of Cocci mold spore growth, hibernation, emergence and transportability off its soil base and into the atmosphere. It will include land/atmosphere modeling to simulate the Cocci environment, from soil wetness and temperature, to wind direction and velocity upon which the mold spores ride, to the moisture and solar radiation it encounters in the free atmosphere, all the way to its destination, availability for inhalation, and deposition—perhaps to begin a new source for the Cocci fungal growth. Atmospheric models and detailed satellite-based observations will permit exploration of Cocci conditions and risk under new weather conditions in new and different climate scenarios.

The proximate belief that Valley fever policy and atmospheric science are within reach of an operational warning and advisory system may be traced through three key publications: from a means to identify with greater confidence where Coccidioides thrive and how atmosphere/land models can forecast and simulate patterns of downwind risk (Sprigg, et al., 2014); an implementation strategy for a Global Dust Health Early Warning System (Sprigg, 2016); and the UNEP, et al. (2016) response to the UN Secretary General's concern of health and other harms from sand and dust storms. The UNEP, WMO and UNCCD endorsed the proposed DHEWS and recognized Valley fever as one of the health risks to be confronted.

Another older philosophical interpretation of CM research with respect to publications and citations by scholars might be similar to Plato's "Allegory of the Cave" in his "Republic." According to this allegory, prisoners isolated in a cave with limited lighting could see the shadows of the objects and tried to identify them (Baggott, 2011). This allegory symbolizes the constraints of human knowledge vis a vis truth and reality.

Complex problems of today, those that challenge nations, can be managed with expert input. The coronavirus (COVID-19) pandemic, ocean pollution and climate change come immediately to mind. But when the decision maker hears testimony too deep, too narrow, from too many, the cacophony debilitates. Science has begun to address that: *interdisciplinary* has found legitimacy—not to replace the need for deep dives into scientific disciplines, but to augment them and to share knowledge across historically siloed experts. Now, *transdisciplinary* efforts further focus on the partnership of disciplines, such that big and complex problems are seen clearly from the beginning, and research strategies are better framed. Scientific journals, their editors and reviewers, can play a critical role in this by being more accepting of interdisciplinary and transdisciplinary research. Science journals have an immediate impact on communication up the chain of understanding—from the deep-dive discoveries in pure disciplinary research, to the credibility of expert input to national and international policy.

Coccidioidomycosis, needs inter-and-transdisciplinary science, and the means to communicate up the chain of understanding and across the silos of science.

As this paper is written, dark times continue in a Coronavirus pandemic that had exposed itself in the last days of 2019. Worldwide, lives have changed in how we eat, work, shop, socialize and spend our free time. In the few weeks it took COVID-19 to fly around the globe we realized we had no cure, no vaccine. Science, it is believed, will save us. But please, work quickly.

The Coronavirus has exposed looming and critical challenges. Science and research must evolve without delay to meet not only COVID-19, but challenges yet to come, the proverbial Black Swans, and those challenges already upon us, climate change and global environmental pollution among them.

To avoid COVID-19 contagion we limit face-to-face encounters. Business, research and life's rituals are conducted over the internet. We have entered the digital age. We no longer can 'kick the can down the road' to postpone decisions of digital sovereignty and digital human rights. The fight against Coronavirus asks that society yield in the emergency, to give up freedoms of movement, information and privacy. Government, society and the free media are challenged to soothe nerve endings that exist between them on these sensitive issues.

Investigations will be made of societal impacts of COVID-19 as well as its global implications in the digital future. But is this pandemic not also an opportunity? Perhaps for global cooperation, collective intelligence, building inclusive society and sustainable economies? While COVID-19 has everyone's attention, an opportunity for not-so-subtle science education (e.g. Sprigg, 2020)? Preparation of a new generation of inter-disciplinary and trans-disciplinary science for the next global health crisis?

The thesis raised in this paper is that these challenges demand research that takes full, immediate advantage of traditionally separated scientific disciplines. Our example is a guide through the study of coccidioidomycosis. It recognizes that one-dimensional studies wait for other one-dimensional studies to be integrated in order to effect understanding and affect policy. This takes time, a luxury unacceptable in the current pandemic.

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**Notes:**

/1/ Damage of the pharyngeal mucosa allows colonization by virulent meningococcus. In some cases, dry climates have been implicated. Could not inhaled and ingested aeolian Saharan dust create similar damage?

/2/ The year 2017 has been calculated for the first 6 months of this year.

/3/ In *Andrea del Sarto,* by Robert Browning

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