

Coccidioidomycosis in the United States

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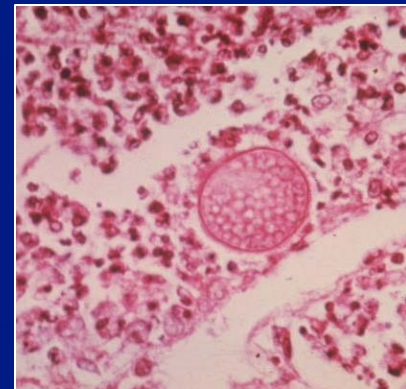
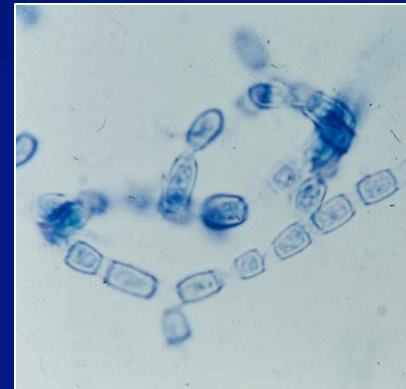
Mycotic Diseases Branch
Centers for Disease Control and Prevention

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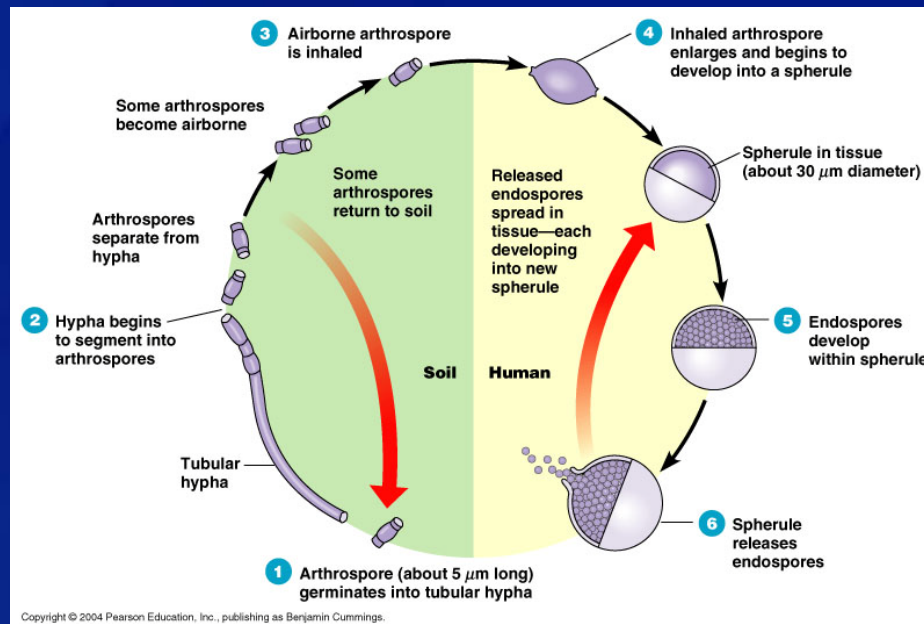
Coccidioides spp.

- **Dimorphic fungus**
 - In environment: mold with single-celled arthrospores
 - In human body: spherule filled with endospores
- **Two species causing disease:**
 - *C. immitis* in California
 - *C. posadasii* elsewhere
- **Persist in soil of endemic areas, typically warm, arid regions with low annual rainfall**

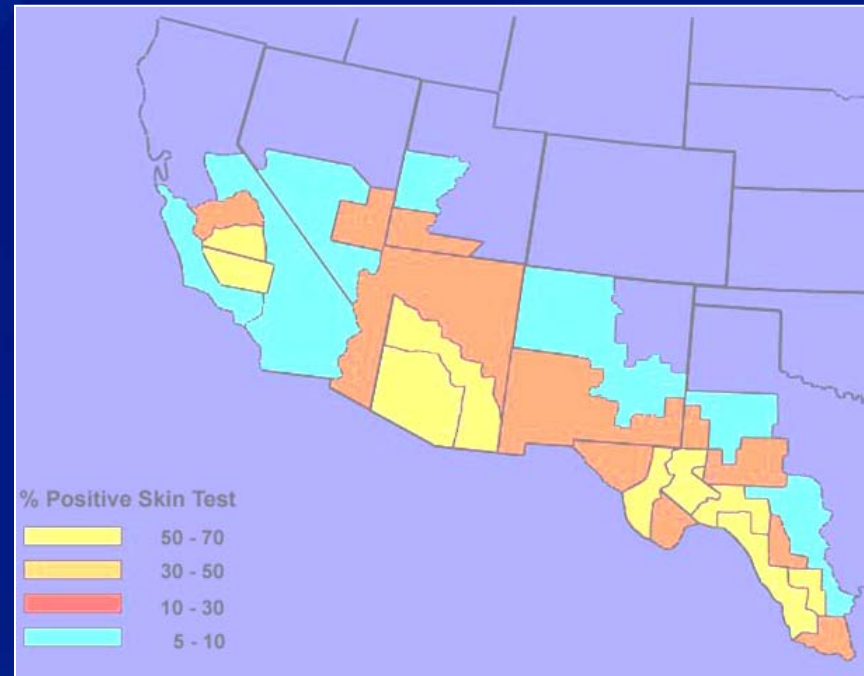


Coccidioidomycosis

- Commonly referred to as “Valley Fever”
- Disease caused when spores inhaled, frequently after a soil disruption
- NO person-to-person transmission



Endemic Areas



- 150,000 infections in US each year
- 50,000 symptomatic infections
- 60% of all US cases in Arizona

100 persons infected
with coccidioidomycosis

~1-3 weeks

~35-50 develop primary
pulmonary disease; the
rest subclinical (protection
from future disease)

~3-12 months (later, if reactivation)

- Chronic pulmonary disease in 5-10 individuals
- Disseminated disease in ~1 individual
- Higher rates of chronic pulmonary, disseminated disease if patients are nonwhite, immunosuppressed (HIV or SOT), or pregnant

Pulmonary disease can be acute and self-limiting, or chronic/progressive

- **Primary pulmonary disease**
 - Resembles influenza or community-acquired pneumonia
 - Cough, fatigue, fever, infiltrate on CXR
 - Usually acute, self-limited
- **Chronic pulmonary disease**
 - Residual nodules, thin-walled cavities
 - Most disappear in ~2 years; hemoptysis may occur in ~25%
 - Chronic symptoms, cavitary lesions with infiltrates, may mimic TB



Musil et al, 2008

Broad spectrum of disseminated disease

- **Cutaneous, subcutaneous common**
 - Varied appearance
- **Joints, soft tissue may be affected (arthritis)**
- **Osteomyelitis: ~40% with disseminated disease**
 - Spine, ribs, cranial bones, long bone ends
 - Persistent, dull pain
- **Meninges: 30-50% with disseminated disease**
 - Mortality rate >90% if untreated



www.humenhealth.com

Risk factors for dissemination

- **Race/ ethnicity**
 - Black, some Asians (Filipinos)
- **3rd trimester of pregnancy**
- **Immunosuppression**
 - HIV
 - Corticosteroids
 - Organ transplantation

Diagnosis of disease

- **Immunodiffusion (ID) tests**
 - Positive = recent or active infection
 - Sensitivity reduced early in infection
- **EIA test (Meridian)**
 - More sensitive than ID?
 - Performance unproven
- **Complement fixation**
- **Culture of sputum: difficult because patients' coughs often nonproductive**
- **PCR of sputum? – may aid early diagnosis**

Treatment of Pulmonary Disease

- Most patients with uncomplicated infection will recover eventually with or without treatment
- IDSA guidelines recommend 200-400 mg/d azole for:
 - Persons with severe symptoms
 - Persons at risk for dissemination (nonwhite, immunosuppressed, pregnant)
 - For others, no guidance
- Amphotericin B may be used with respiratory failure, rapidly progressive infections

Treatment of Disseminated Disease

- **Disseminated non-meningeal**
 - Azole or Amphotericin B, depending on clinical picture
- **Disseminated meningeal**
 - Fluconazole or itraconazole
 - Some clinicians start with high dose (800-1000 mg/day)
- **Voriconazole, posaconazole may also be beneficial**
- **Surgical interventions may be needed (pulmonary cavities, shunts)**
- **Patients with disseminated disease should be treated indefinitely due to high relapse rates**

Best treatment unclear

- ***No data from clinical trials to evaluate symptom relief or prevention of relapse: need for proven treatment strategies***
- **Studies of azole with early cocci pneumonia:**
 - No difference between treated and untreated groups; complications only in treated group, after drug d/c
 - Treatment failure in 20-40%; relapse rates high among those who improved during treatment
 - New treatment? Nikkomycin Z, Phase II trials

Is it possible to prevent infection?

- **Risky activities exist (digging, etc.)**
- **Most acquire disease simply by breathing**
- **Since exposure can't be eliminated, only measure available to prevent infection is a vaccine**
 - **NO VACCINE currently**

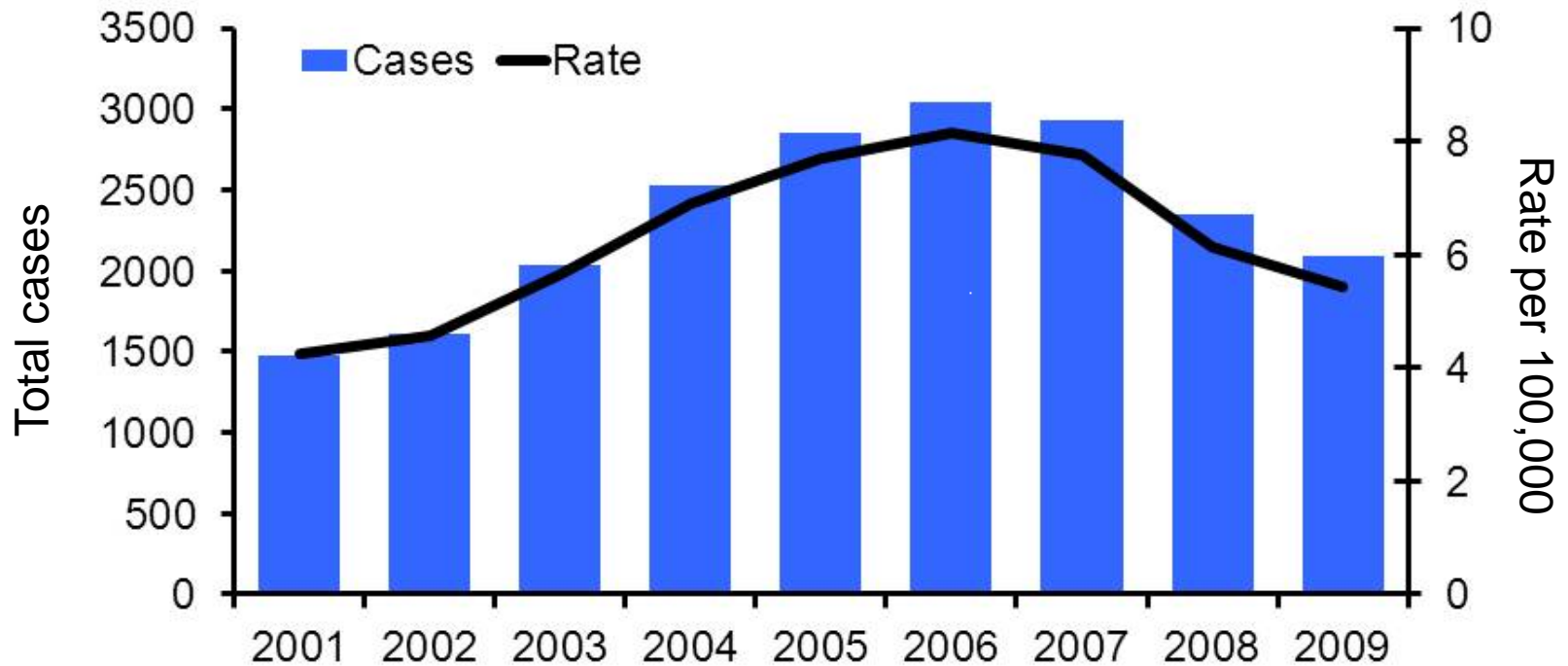
Vaccine?

- **Rationale: immunity from cocci is lifelong**
- **Initial whole-spherule and whole-mycelial vaccines nonimmunogenic in human trials**
 - Focus now on live attenuated, recombinant vaccines
- **Cost-effectiveness uncertain**
 - Focus on high-risk groups?
 - Construction, miners, landscapers, immunocompromised patients
 - Military (training recruits who are temporary residents)

Surveillance for cocci in California

- **Passive surveillance for cases and outbreaks**
- **Case definition based on CSTE definition**
 - **Clinical criteria**
 - Flu-like illness
 - Pneumonia, other pulmonary lesion, or meningitis
 - Rash
 - Bones, joints, skin involvement
 - Involvement of viscera or lymph nodes
 - **Lab evidence of infection**
 - Culture, histopathologic, molecular, or immunologic evidence of infection

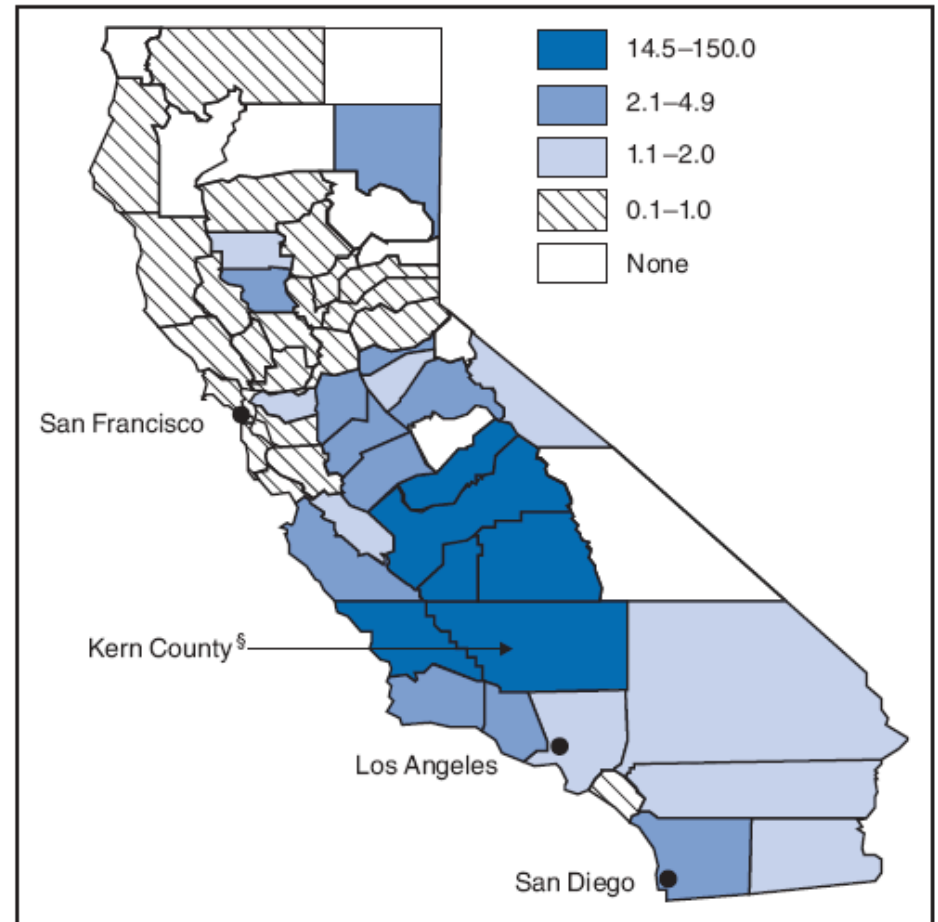
Rates of reported Valley Fever in California, 2001-2009



Reported cocci in California, 2001-2009

- Rates vary widely by county
- 65% male
- Rates highest in 20-50 yo
- Highest rates in Hispanics, Blacks

FIGURE 2. Average annual rate* of reported cases of coccidioidomycosis, by county — California, 2000–2007†



* Per 100,000 population.

Surveillance for cocci in Arizona

- **Mandatory reporting from laboratories beginning in 1997**
 - ~5,000 cases reported each year using lab-only reporting
- **Two major commercial labs report 46% of cases in AZ**
 - One lab required both EIA and complement fixation / immunodiffusion for positive results; beginning in 2009, reporting changed to only require EIA
 - As a result, case reports increased in 2009

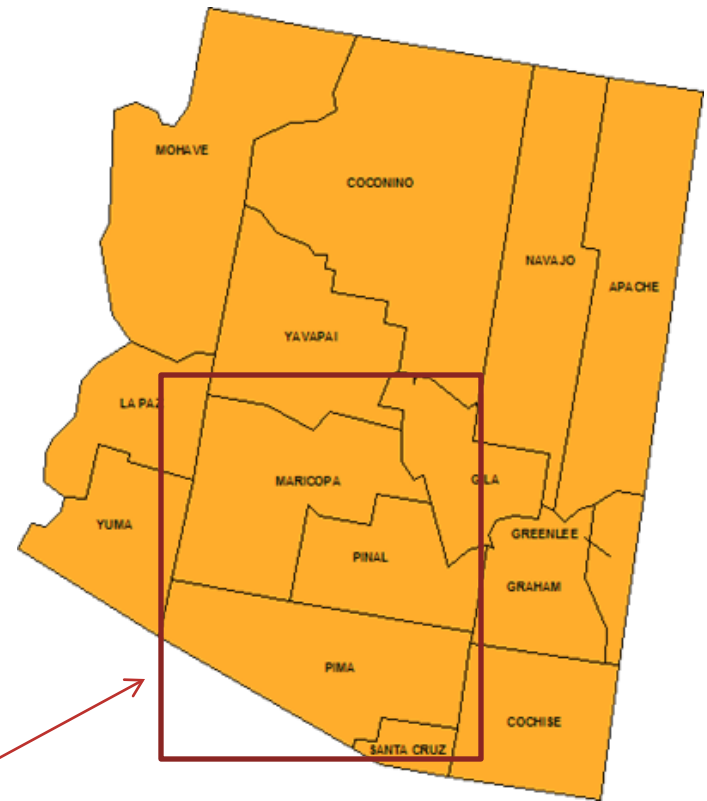
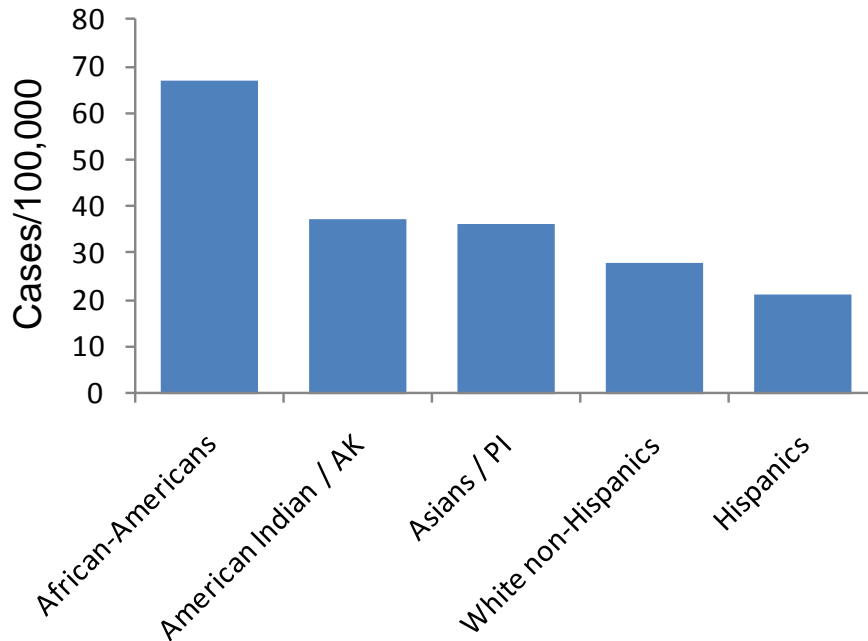
Rates of reported Valley Fever in Arizona, 1990-2009



AZDHS.gov/phs/oids; Hector, 2011

*2 major commercial labs account for 46% of all cocci reporting to AZ State HD

Reported cocci in AZ, 2009



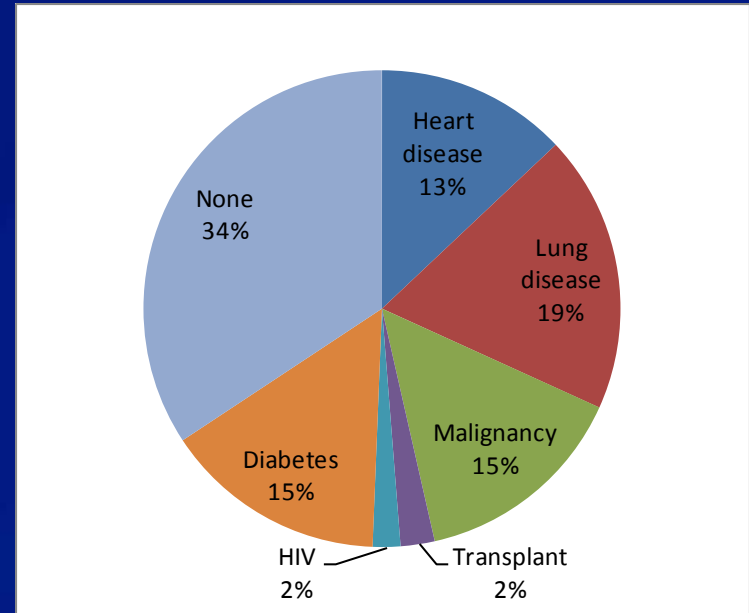
- 55% female (45% female 2006-8)
- Rates highest in >65 yo
- Highest rates in most populous counties (Maricopa, Pima, Pinal)

Enhanced surveillance for cocci, AZ

- **Objectives**
 - To validate the laboratory-based case definition
 - To understand more about the public health burden of cocci
- **Contacted every 10th cocci case by mail, interviewed by telephone (n=493 patients)**

Patients (N=493)

- **Common symptoms:**
 - Fatigue (84%)
 - Cough (67%)
 - Dyspnea (59%)
 - Fever (54%)
- **Symptoms lasted median of 120 days**
 - 42 days among recovered cases (40%)
 - 157 days among non-recovered cases (60%)
- **469 (95%) met CSTE case definition**



**Underlying conditions
among enhanced
surveillance patients**

Delays in diagnosis, impact on patients

- **Healthcare sought median of 11 days after onset**
- **Among employed, 74% missed work due to cocci**
 - **Median workdays missed: 14**
- **75% unable to do activities of daily living (ADLs) at some point during illness**
 - **Median days unable to perform ADLs: 47**

Impact on Healthcare System

- 46% went to the ER for Valley Fever
- 41% were hospitalized, median of six days
- 26% saw their doctor 10+ times during illness
- 1,093 hospital visits with primary dx of cocci in 2007
 - Over **59 million dollars in hospital charges**
 - Median \$33K / visit

Cocci is underdiagnosed

- **Three separate studies in Arizona have shown that cocci may cause 10-30% of CAP!***
 - If cocci represents a large % of CAP, could be many cases/year (>50,000?)
 - ~5,000 reported to health dept in AZ each year
 - How frequently is CAP tested for cocci?

Testing Practices Among Patients with CAP – Metropolitan Phoenix, 2003-2004

- **Objectives**

- Estimate the proportion of patients presenting to clinics with pneumonia who are tested for cocci
- Determine predictors of cocci among CAP patients
- Understand provider testing practices in Maricopa County

- **Methods**

- Retrospective cohort studies in two distinct outpatient populations (Healthcare Systems A and B)
 - Chart review to determine % of CAP patients tested for cocci

Study locations

	System A	System B
Primary care	Yes	Yes
Subspecialty care	Yes	Yes
Community health centers	13	17
Associated with hospital	Yes (Public)	No
Racial /ethnic minorities	Majority	N/A
Insurance	Many without private insurance	Almost exclusively privately insured

Few CAP patients tested for cocci overall...and serological testing more likely in private vs public healthcare system

Cocci testing	System A (n=66 CAP cases)	System B (n=87 CAP cases)	p
Serology at any CAP visit	1 (2)	11 (13)	<0.05
Diagnosis of cocci	0 (0)	1 (1)	NS
Days until testing (median)	12	27 (1-99)	-
Symptoms ≥ 14 days before test	0 (0)	7 (64%)	NS

Few clinical differences between CAP patients who test positive vs negative for cocci

Characteristic	Positive Cocci Serology (n=9)	Negative Cocci Serology (n=134)	p
Mean age (range), years	41.4 (20-82)	42.0 (14-91)	NS
Male	6 (66.7)	66 (49.3)	NS
Black/ African-American	3 (33.3)	9 (6.7)	NS
Smoking Past or Present	3 (33.3)	64 (47.7)	NS
Cough	8 (88.9)	125 (93.3)	NS
Fever	5 (55.6)	119 (88.8)	0.02
Chest Pain	2 (22.2)	65 (48.5)	NS
Dyspnea	2 (22.2)	46 (34.3)	NS
Fatigue	1 (11.1)	18 (13.4)	NS
Rash	0 (0)	1 (0.8)	NS
Symptom duration (days)	11.6 (2-35)	10.4 (1-182)	NS

Longer duration of symptoms made testing for cocci more likely

Characteristic	Tested (n=125)	Not Tested (n=260)	p
Days of sx (mean, range)	11 (1-182)	6 (1-90)	0.01
Age (mean, range), years	42 (14-91)	40(13-91)	NS
Male	72 (50%)	147 (52%)	NS
White Non-Hispanic	87 (61%)	153 (54%)	
Hispanic/ Latino	30 (21%)	83 (29%)	NS
Smoking history	67 (47%)	114 (40%)	NS

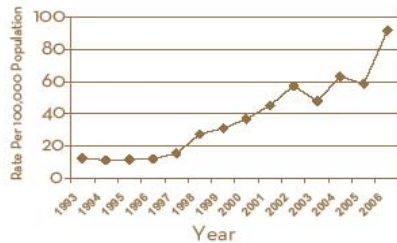
Conclusions

- **Coccidiomycosis causes a significant health and quality-of-life burden for patients**
 - The economic impact of each case on the patient and on the healthcare system is substantial
- **High proportion of CAP probably attributable to cocci**
 - Low levels of testing in CAP patients (2-13%?)
 - Symptom differences, symptom duration do not help distinguish cocci from other CAP; thus, lab testing is needed for diagnosis
- **No vaccine and existing treatment is not optimal; need for proven treatments**

Ongoing Physician Education in AZ

VALLEY FEVER CASES ARE INCREASING

Coccidioidomycosis rate per 100,000 population by year, Arizona -1993-2006



VALLEY FEVER MIMICS COMMUNITY ACQUIRED PNEUMONIA (CAP)

29% of Ambulatory CAP cases in Tucson, Arizona had diagnosis of Valley Fever.

Valdivia L, Nix D, Wright M, et al.
Coccidioidomycosis as a Common Cause of Community Acquired Pneumonia. *Emerging Infectious Diseases* 2004; 12: 958-62.



WHAT CAN YOU DO?

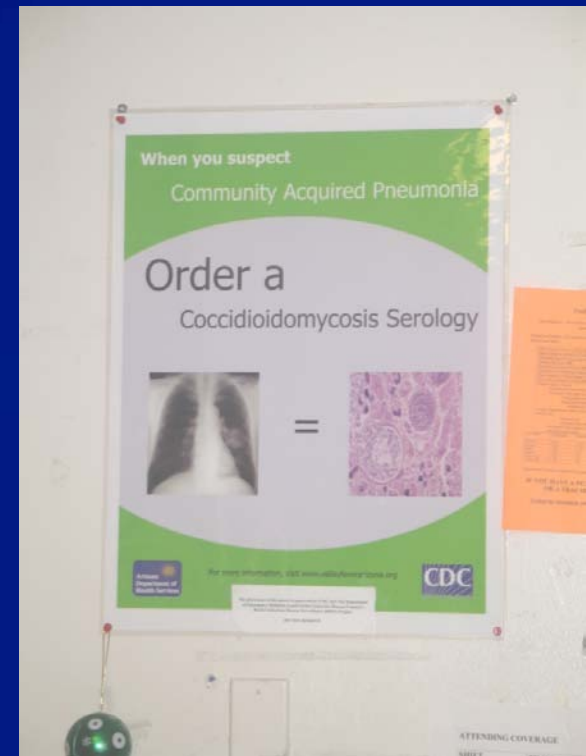
- Order Cocci serology on CAP cases
- Manage Valley fever cases
 - Inform patient of diagnosis
 - Report the case to public health
 - Consider treatment with anti-fungal drugs if the patient is at risk for severe disease

For more information on treatment guidelines, visit www.idsociety.org/pg

Resources

Arizona Department of Health Services
Office of Infectious Disease Services
150 N. 18th Ave, Suite 140
Phoenix, Arizona 85007
(602) 364-4562
www.valleyfeverarizona.com

Valley Fever Center for Excellence
Mail Stop 11111NF
3601 S. 6th Avenue
Tucson, Arizona 85723
Hotline: (520) 429-4777
<http://www.vfcec.arizona.edu/>



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Thank You

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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

National Center for Emerging and Zoonotic Infectious Diseases

Division of Foodborne, Waterborne, and Environmental Diseases

