# Coccidiodomycosis in the United States

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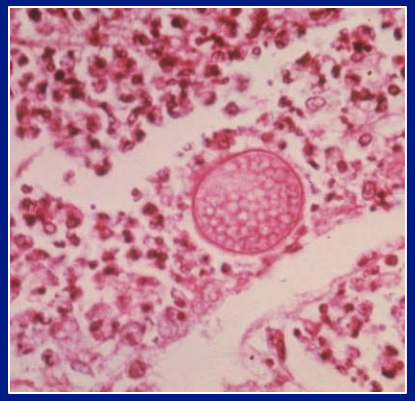
National Center for Emerging and Zoonotic Infectious Diseases
Division of Foodborne, Waterborne, and Envrionmental Diseases

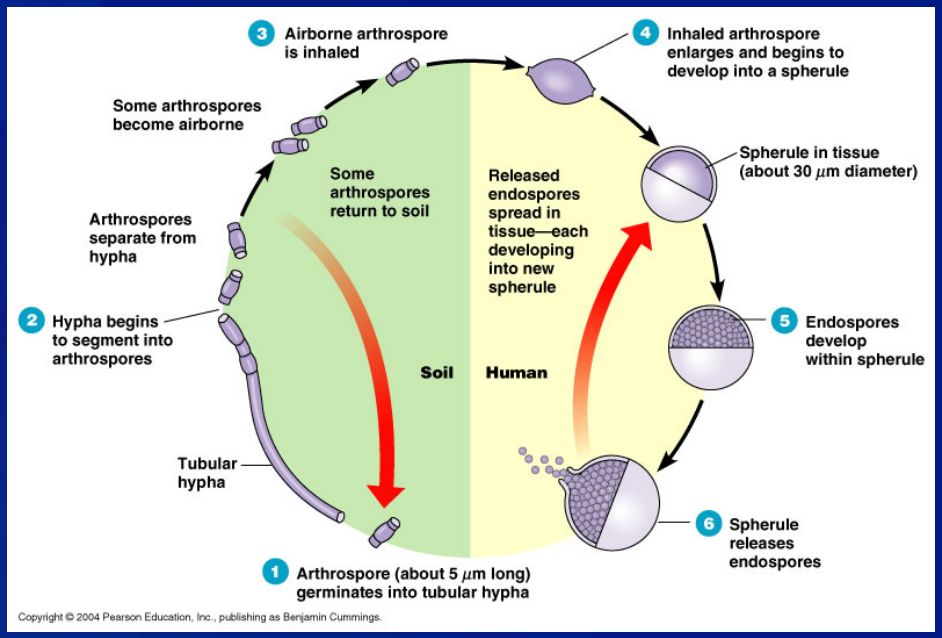
# *Coccidiodes spp.*

- **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**

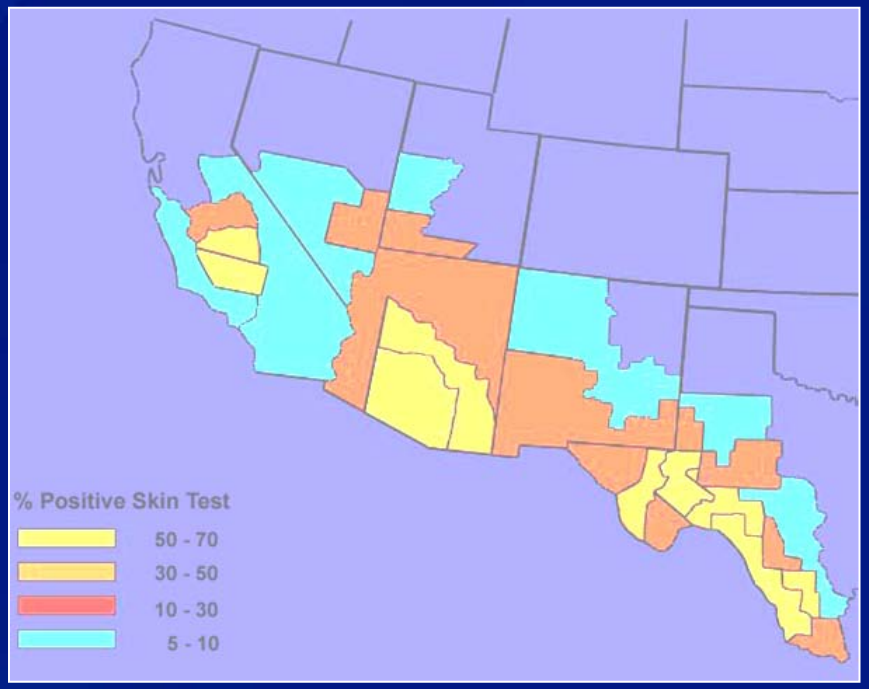


# Coccidiodomycosis

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

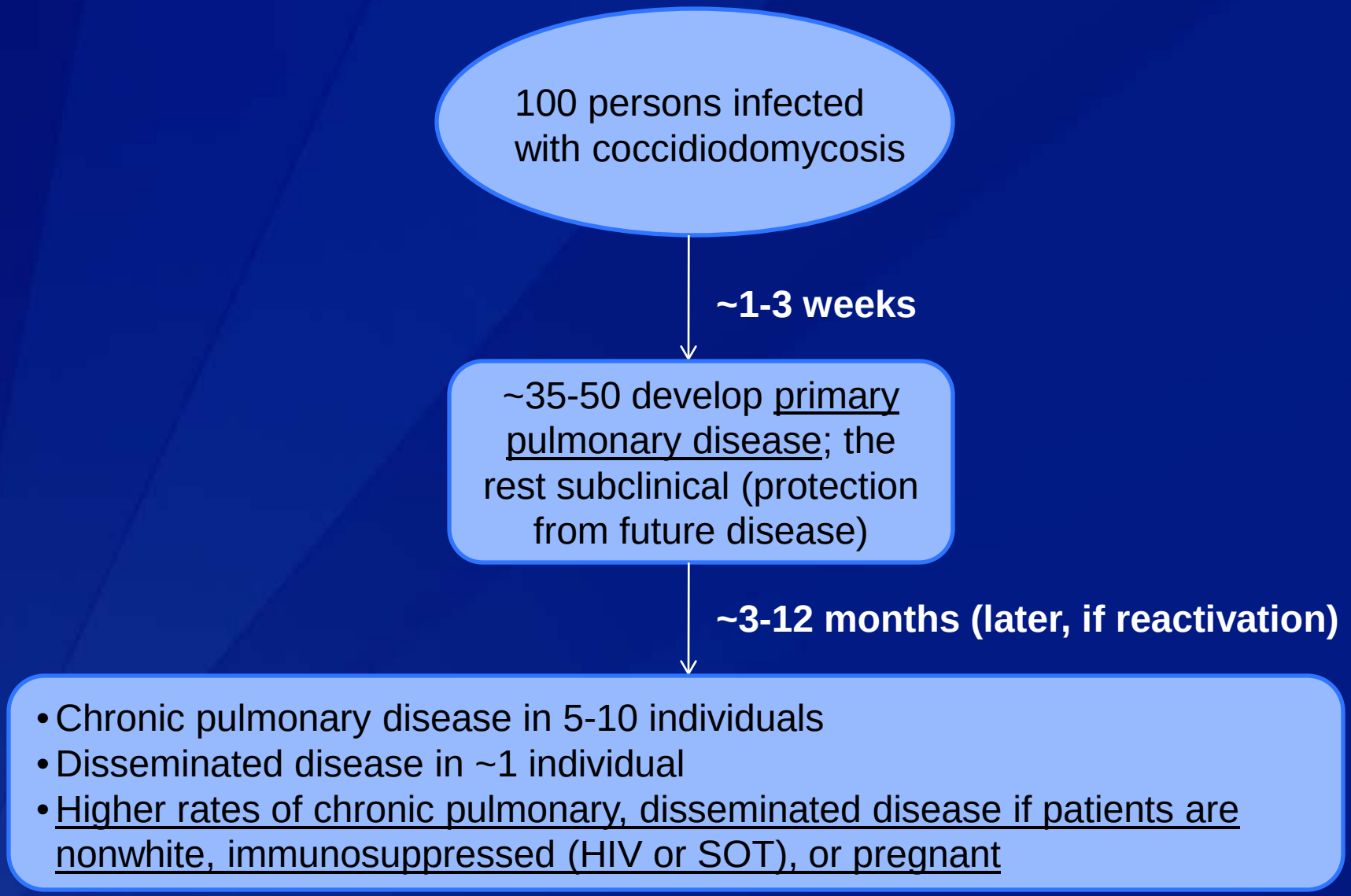


# Endemic Areas


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

*Galgiani, CID 2005*


100 persons infected with coccidiodomycosis
~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)
- Vorizconazole, 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

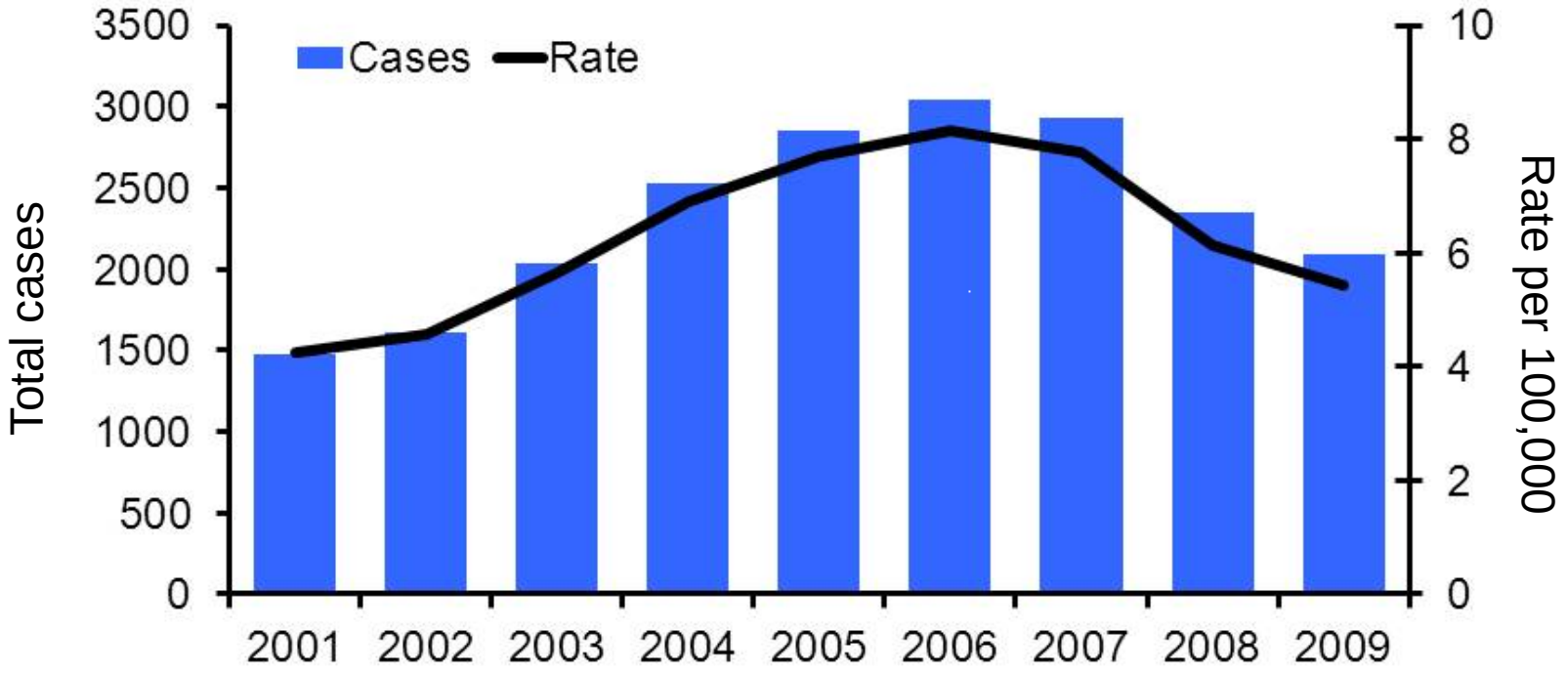
# Vaccine?

- 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

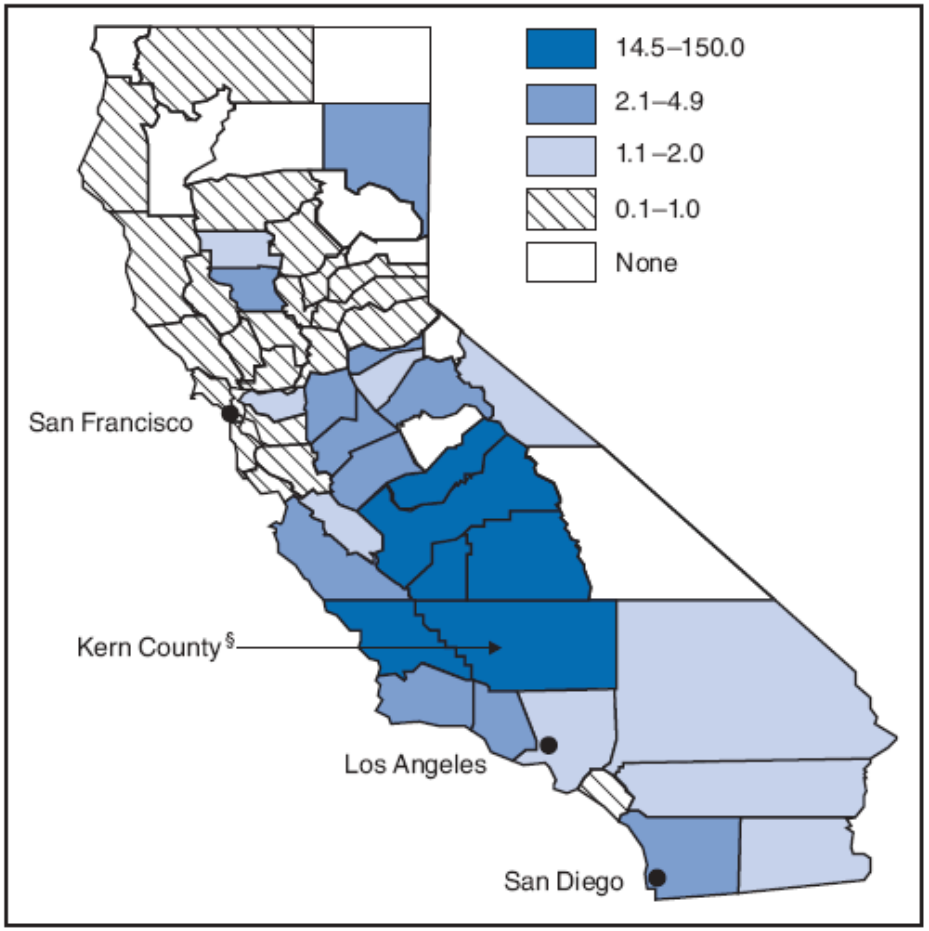



Hector, 2011

# 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†



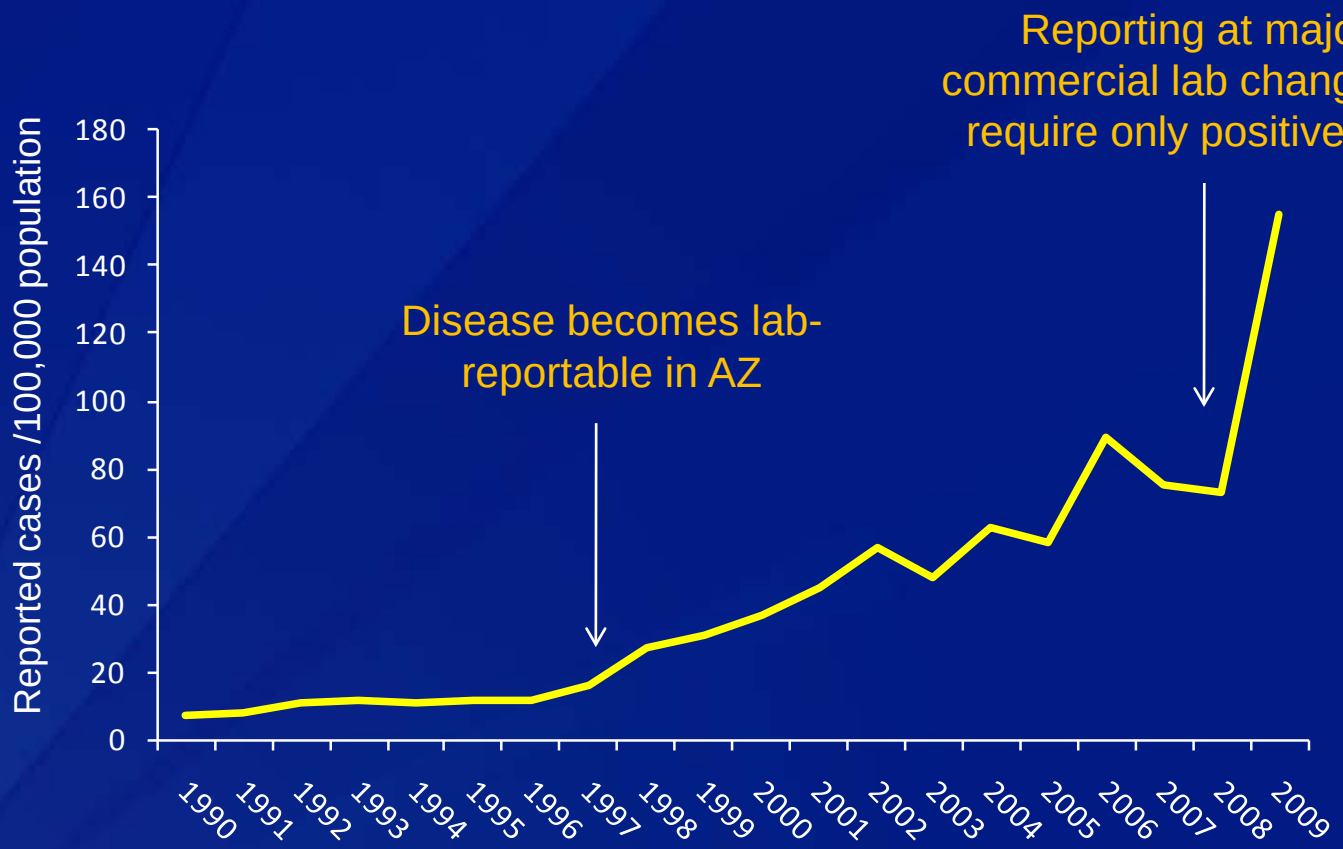

* Per 100,000 population.

Vugia, MMWR, 2009

# 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**

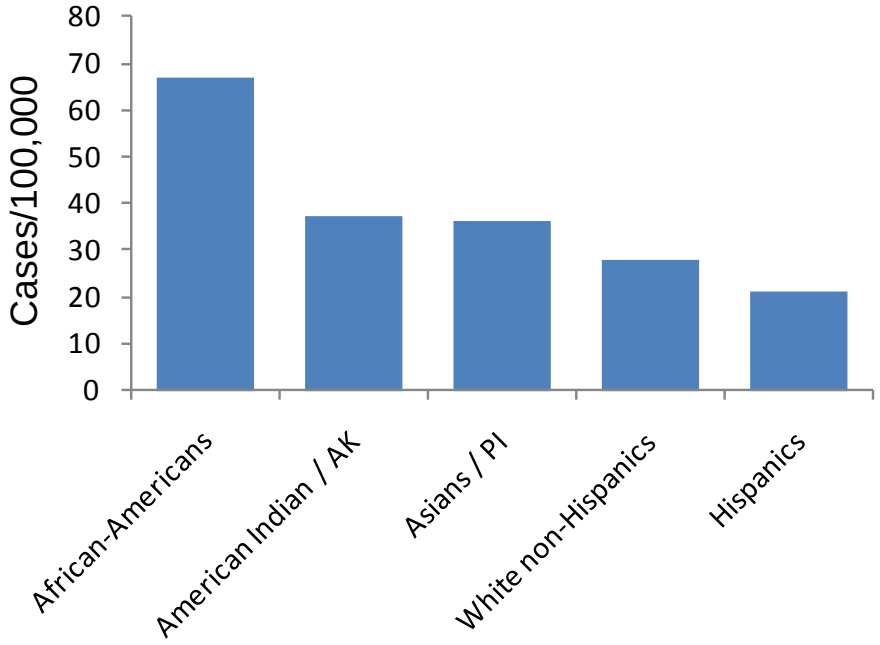
# Rates of reported Valley Fever in Arizona, 1990-2009

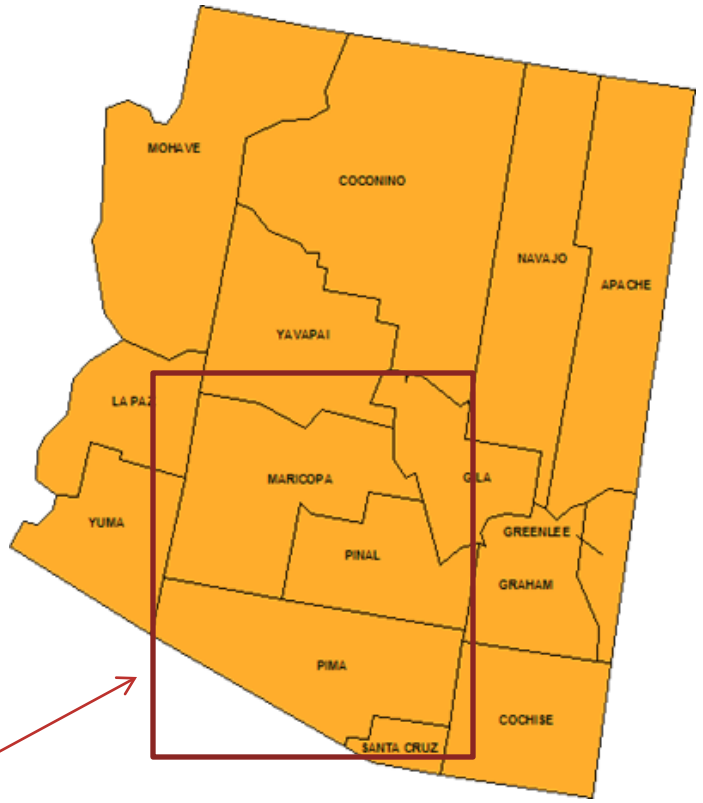



AZDHS.gov/phs/oids; Hector, 2011

*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)

Hector, 2011

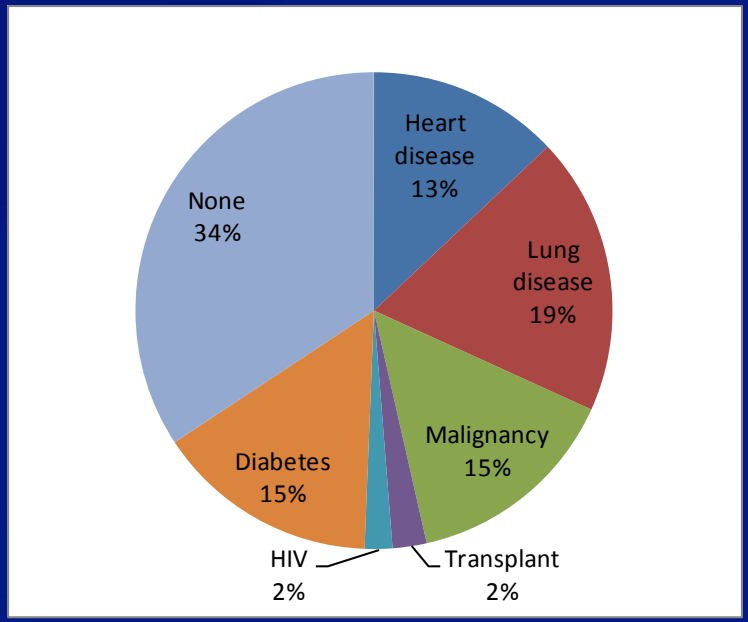
# Enhanced surveillance for cocci, AZ

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

Tsang *et al*, EID 2010; Sunenshine *et al*, Cocci Study Group 2008

# 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?**

*Valdivia, Emerg Infect Dis 2006; Campion, AZ Geriatrics Soc J, 2003; Chang DC et al, EID 2008

# 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

*Chang, DC et al, EID 2008

# 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%) | NS |
| Hispanic/ Latino | 30 (21%) | 83 (29%) | |
| Smoking history | 67 (47%) | 114 (40%) | NS |

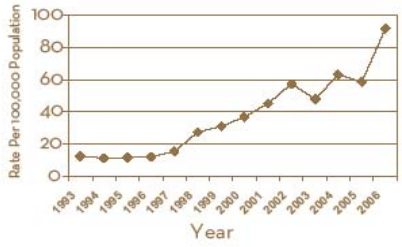
# Conclusions

- **Coccidiodomycosis 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; <u>need for proven treatments</u>**

# Ongoing Physician Education in AZ

## VALLEY FEVER CASES ARE INCREASING

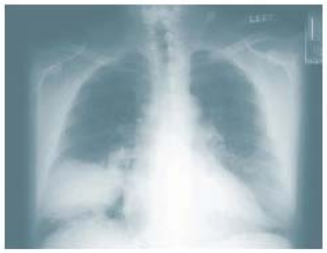
Coccidioidomycosis rate per 100,000 population by year, Arizona -1993-2006




## 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 2006; 12: 958-62



## WHAT CAN YOU DO?

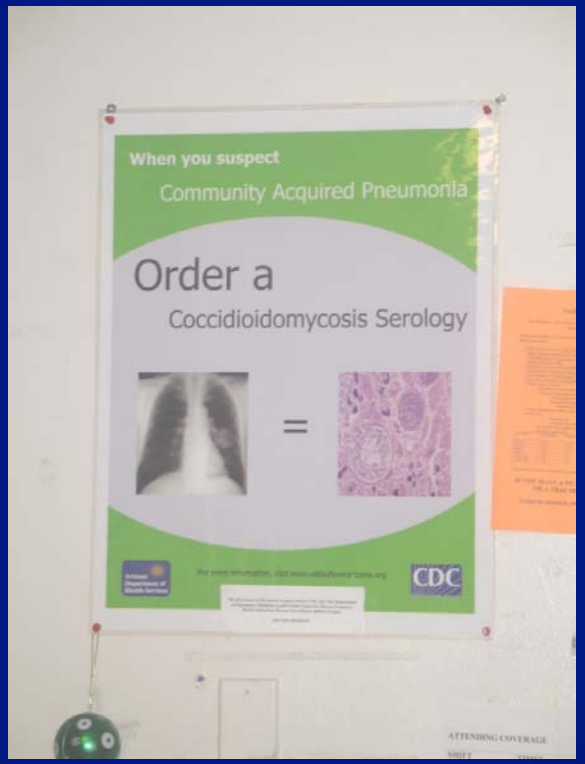
- Order Cocci serology on CAP cases
- Manage Valley fever cases
  - Inform patient of diagnosis
  - Report the case to public health
  - Consider treatment with anti-fungal drugs if the patient is at risk for severe disease

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.org

Valley Fever Center for Excellence
Mail Stop 111INF
3601 S. 6th Avenue
Tucson, Arizona 85723
Hotline: (520) 629-4777
http://www.vfce.arizona.edu/



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# Thank You

**For more information please contact Centers for Disease Control and Prevention**
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E-mail: cdcinfo@cdc.gov  Web: www.cdc.gov