Coccidioidomycosis: An Emerging Health Burden

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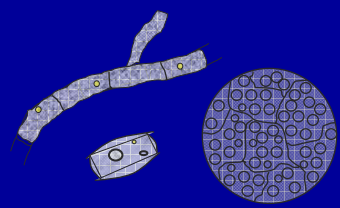


Valley Fever Vaccine Project

Descriptive Epidemiology

- U.S. population at risk ~30 million, including central and southern California and most of Arizona, parts of NM, TX, UT, NV
- 130,000-150,000 new infections/yr
  - 40,000-60,000 cases of primary disease (6,000+ reported)
  - 3,500 cases of disseminated disease
  - 200 deaths per year

MMWR Feb. 13, 2009: Increase in coccidioidomycosis---California 2000-2007

90% of cases occur in AZ and California

Historically, the number of cases was usually cited at 100,000/yr, but now higher figures are being cited

CDC Case Definition: 2008

One or more of:

- Influenza-like signs and symptoms (e.g., fever, chest pain, cough, myalgia, arthralgia, and headache)
- Pneumonia or other pulmonary lesion, diagnosed by chest radiograph
- Erythema nodosum or erythema multiforme rash
- Involvement of bones, joints, or skin by dissemination
- Meningitis
- Involvement of viscera and lymph nodes

http://www.cdc.gov/ncphi/disss/nndss/casedef/coccidioid2008.htm

Disease always starts as a pulmonary infection, but all too often the dx isn't made until signs of overt dissemination occur

CDC Laboratory Criteria for Dx- 2008

- Cultural, histopathologic, or molecular evidence of presence of *Coccidioides* species, or
- Positive serologic test for coccidioidal antibodies in serum, cerebrospinal fluid, or other body fluids by:
  1. Detection of coccidioidal IgM by immunodiffusion, enzyme immunoassay (EIA), latex agglutination, or tube precipitin, or
  2. Detection of coccidioidal IgG (not rising titer!) by immunodiffusion, EIA, or comp. fixation, or
- Coccidioidal skin-test conversion from negative to positive after onset of clinical signs and symptoms

http://www.cdc.gov/ncphi/disss/nndss/casedef/coccidioid2008.htm

Serologies for cocci are “solid”; particularly in good labs

What has changed is the standard for a single sample detection of IgG, and not rising titers from repeat sampling

Risk Factors

- **For acquiring infection:**
  - Exposure to dust during dry and windy season
  - Exposure to soil or fomites - excavations, construction
- **For developing dissemination:**
  - Race/ethnicity, genetic factors
    - 1979 dust storm: Filipinos - 67%, Blacks - 54%, Whites – 11%, Asians - 36%*
    - Blood group B and certain HLA II alleles associated with dissemination/resistance
  - Pregnancy
  - Age
  - Immunosuppression (diabetes mellitus, HIV, organ transplantation)

* Pappagianis D, Lindsay S, Beall S, Williams P. Ethnic background and the clinical course of coccidioidomycosis. Am Rev Resp Dis. 1979 Oct;120(4):959-61.

Single cases are acquired from inhalation of dust

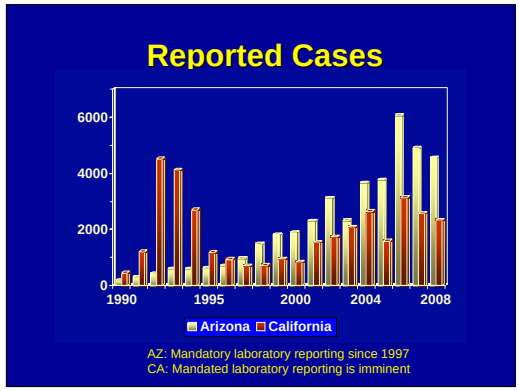
Outbreaks are usually associated with displacement of volumes of dirt. It has to do with where the fungus lives; usually 6” or more below the surface, or in rodent burrows

The ‘79 dust storm was tailor-made for epidemiologists; a defined period of exposure to large numbers of spores (40 million tons of topsoil was displaced) in a defined area north to Red Bluff and west to SF; and during a period when there was typically little outdoor occupational activity (Dec 20)

10 days to 3 weeks later, all hell broke loose; thousands of serology samples were submitted. Patients were followed closely; high rates of dissemination generally confirmed that Filipinos>Blacks>Whites/Asians (few Hispanics in the population of disseminated patients)

Pregancy: used to be a leading cause of maternal mortality- abortion or death; not the fatal outcome it once was- ampho B

Immunosuppression: organ recipients and even infected organs are a problem, but management has improved



Epidemic of '90's: 2/3 of cases were in Kern County. Dissemination was 4-5% Hospitalization costs: $36 million & Total economic impact estimated at $56 million for 3 years

More recent reports: Although Valley Fever is greatly under-reported, the trend of these statistics clearly on the rise.

MMWR 2-13-09: During 1995--2000, the number of reported coccidioidomycosis cases in California averaged 2.5 per 100,000 population annually. However, from 2000 to 2006, the incidence rate more than tripled, increasing from 2.4 to 8.0 per 100,000 population. To characterize this increase, the California Department of Public Health analyzed case and hospitalization data for the period 2000--2007 and preliminary case report data for 2008.

The results indicated that, during 2000--2006, the number of reported cases and hospitalizations for coccidioidomycosis in California increased each year to a rate of 4.3 per 100,000, before decreasing in 2007.

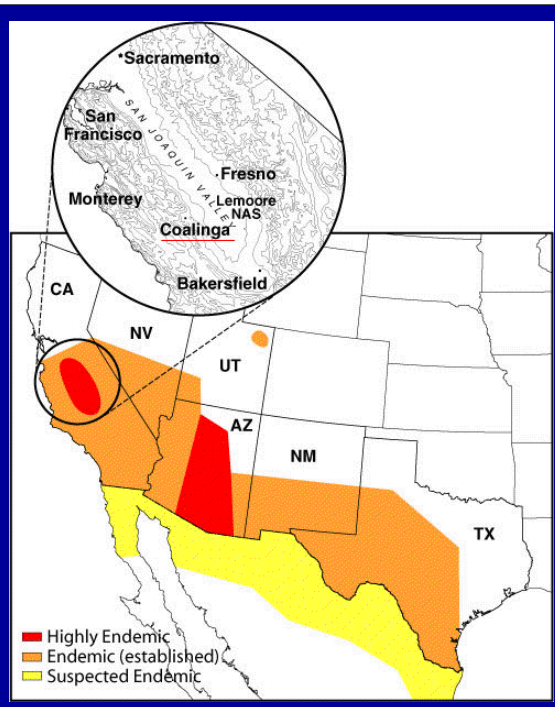
Annual incidence during 2000--2007 was highest in Kern County (150.0 cases per 100,000 population; population increased 19% in that period), and the hospitalization rate was highest among blacks, increasing from 3.0 to 7.5 per 100,000 population.

In 2009; cases appear to be increasing: AZ: 4200 cases Jan-July, nearly equaling total for '08 CA: 1350 cases

Why is the incidence of clinical coccidioidomycosis increasing?

Pleasant Valley State Prison: the canary in the coal mine?

Crum N, Lamb C, Utz G, Amundson D, Wallace M. Coccidioidomycosis outbreak among United States Navy SEALs training in a *Coccidioides immitis*-endemic area-Coalinga, California. J Infect Dis. 2002 186(6):865-868



23 Navy Seals sent for sniper training at a private rifle range in Sept ‘01.

6 weeks; bivouaced on the range and did what Navy Seal snipers do: dig fox holes, crawl through the dirt, discharge weapons and blow things up.

By October, 6 had presented at a local clinic. Upon investigation, it was determined that 10 (44%) had acquired cocci.

Coalinga has long been known to be an area of hyperendemicity for cocci, but the attack rate was unprecedented.

Reported Cases: Fresno County

	Reported Cases			
Year	Fresno County Total	Coalinga Civilian	PVSP	Prison % of County Cases
2002	84	4	47	56
2003	140	23	107	76
2004	122	6	70	57
2005	290	18	241	83
2006	776	154	520	67
2007	450	17	325	72
2008	310	85	159	51
2009*	280	51	173	62

* Through May 2009

Census: PVSP- 5000 ('02: 4600; '05: 4900; '06:5100; designed for 2600)
Coalinga- 11,000 Fresno Co- approx. 950,000

PVSP 2005 Attack rate: 4912/100,000 PVSP 2006 Attack rate: 10,400/100,000

Coalinga 2005: 129/100,000 (40-fold less) Coalinga 2006: 1400/100,000

Kern 1992 attack rate: 572/100,000 (18-fold less than PVSP '06)

Burden & Costs (est) PVSP in 2005

- **166 inmates met case def; 142 treated***
  - Many did not meet IDSA guidelines
  - Diflucan: $250,000-500,000
- **142 inmates had X-rays***
- **29 inmates hospitalized (18% of cases)***
  - $900,000 (based on est. $30k/civilian patient)
  - Inmates are hospitalized in community hospitals, requiring 24/7 guard & associated personnel expense!
- **4 deaths (and 1 prison guard)**

*CA EPI 06-02 Coccidioidomycosis Outbreak at a State Prison-2005. DHS 1/11/2007

Not every inmate with a positive serology gets treated. Treatment, once initiated, is 90 days to several months in duration. Expenses associated with distribution of meds, regular serologies and medical visits

Each hospitalized inmate requires a guard be present in the hospital; months of additional expense for CDCR!

2005 cases may have cost PVSP as much as $3 million; 2006 may have cost $5 million, or 2-3% of their annual operating budget!

What is happening in PVSP?

- The peak & trends generally mirror reported cases in CA, but the rates are much, much higher
- DHS report on PVSP 2005 outbreak
  - No surveillance bias
  - Possible contribution of climate, construction in area
  - Black race & outdoor exposure id'ed as risk factors for primary disease
  - Inmates from outside endemic area
  - Concomitant increase in employee cases

No surveillance bias: number of negative samples didn't increase

Rain & PVSP

Year	PVSP Cases	Year	Rainfall Totals
2002	**47**	**01-02**	**3.38Ó**
2003	**107**	**02-03**	**8.75Ó**
2004	**70**	**03-04**	**5.11Ó**
2005	**241**	**04-05**	**13.23Ó***
2006	**520**	**05-06**	**8.46Ó***
2007	**325**	**06-07**	**2.81Ó**
2008	**159**	**07-08**	**7.27Ó***
2009	**173**	**08-09**	**3.38Ó**

* >3Ó in January

Dec ‘04-Jan ‘05: 5.82”
Dec ‘07-Jan ‘08: 5.78”

Rainfall is listed as seasonal; July-June

Dr. Andrew Comire (UA) analyzed the data and concluded there was likely a correlation between high rainfall and increased cases, with a 1 year lag.

The increased rain in Coalinga in Dec-Jan 04-05 predated the uptick in cases at PVSP by almost exactly one year. The increase continued through most of ’06.

The same pattern appears to be repeating in the current year, putting ’09 in line to have the 2nd highest total of cases.

What is the likely source?

The RR soil most certainly harbors the fungus. The terrain is similar around the bowl that surrounds the Valley. The airport shows the general direction of prevailing winds, which blow at 8-15 MPH on a typical summer afternoon.

Both the low hills and the riparian area north of PVSP most certainly harbors squirrels, rabbits and other burrowing animals. Dr. Fred Fisher, who established that Dinosaur National Monument is Lower Sonoran Life Zone & harbors cocci, has stated that animals, not wind, is the mechanism of spread & seeding of soil. Given the topography & fauna, it is just as likely that the arthroconidia come from outside the grounds of PVSP as inside the fenced area of the prison. Thus, dust mitigation efforts on prison grounds may have limited ability to reduce risk of exposure.

Possible Contributing Factors

- **Climate:**
  - **"Compressed" periods of higher rainfall**
- **Increased inmate populations:**
  - **Influx from non-endemic areas**
  - **Prison is at twice the design capacity**
- **Exposure:**
  - **Correlation between lock-down status & reduced incidence in cell blocks**
  - **Extensive construction adjacent to PVSP '02-'05; seeding of adjacent soil?**

Periods of intense rain appear to be contributory, but are not the sole requirement. Bakersfield had its highest total of rainfall in history in '98, and while there was a 55% increase in cases in '99, it didn't match the dramatic 10-fold increases seen in the '92 epidemic.

PVSP may have had 1-2,000 new inmates leading up to the current epidemic; all likely from outside the endemic area. That, plus stress of overcrowding in a dangerous prison environment, plus the increased environmental exposure could all have been factors in the epidemic.

Can coccidioidomycosis be prevented or controlled?

Prevention Options: 2009

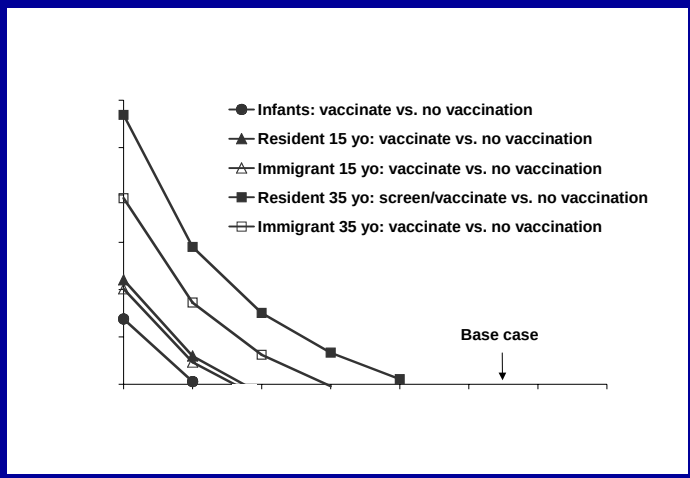
- **Limit exposure to arthroconidia**
  - **Dust control (watering, paving, grass)**
  - **Occupational controls (masks at construction sites)**
- **Early recognition and therapy of primary infection**
- **Vaccine that avoids problems of FKS**
  - **Recovery from infection triggers "solid" immunity**
  - **Spherules trigger reactogenic response**

Dust mitigation methods of the 40's were successful at military bases in the Central Valley. May not work at PVSP if the source is off-site.

No well-controlled clinical trial for treatment of primary cocci has ever been performed. IDSA guideliness do not call for treatment of primary disease in absence of underlying risk factors or severe symptoms.

But…PVSP has seen a dramatic decrease in the numbers of disseminated cases, possibly a result of early detection and treatment.

Cost-Effectiveness of a vaccine



* Barnato et al. Cost-effectiveness of a potential vaccine for coccidioidomycosis. Emerg Infect Dis 2001. 7(5):997-806.

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Amber Barnato was commissioned to perform cost-effectiveness study. Models were constructed and used with assumptions employed with various degrees of stringency

Among children, vaccination saved 1.9 quality-adjusted life days (QALD) and $33 per person. Among adults, screening followed by vaccination saved 0.5 QALD per person and cost $62,000 per QALY (quality of life years) gained over no vaccination.

For adults, the incremental gain from vaccinating all persons compared with screening followed by vaccination contributed an additional 0.05 QALD at a cost of $235,000 per QALY gained.

Barnato Conclusions

- **Cost-effectiveness is higher for infants compared to older age groups**
  (Kern county 2004: <10% cases 0-14 yrs)
- **A vaccine could significantly reduce the public health burden of disease**
- **Vaccine must be safe and have high degree of efficacy in order to be utilized**

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But children don't tend to acquire this disease, and if they do, they tend to handle it rather well.

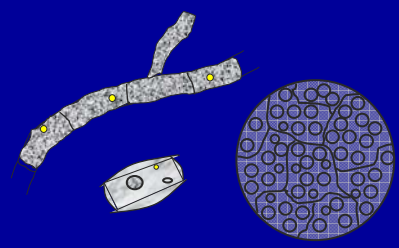
Those of an older demographic category; 1) come down with the disease; and 2) are disproportionately more likely to be hospitalized

This isn't a contagious disease and most people handle infection.

One can legitimately ask the question, could you effectively vaccinate a highly susceptible person to prevent primary disease and/or dissemination?

Vaccine Status

- Recombinant protein vaccine confers protection, but…
  - Breakthroughs at higher infection levels
  - Problems with protein expression
  - Lack of good adjuvants for CMI, Th1
- Attenuated vaccine
  - Good protection
  - Low reactogenicity
  - Is it safe to vaccinate for a non-contagious diseases with live vaccine?



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