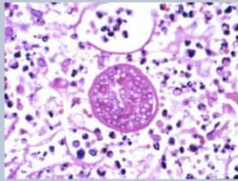


# Specificity of Enzyme Immunoassay for Serologic Coccidioidomycosis Diagnosis Compared to Immunodiffusion

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Spherule (found in the lungs)

## Coccidioidomycosis (Valley Fever)

- Respiratory infection caused by soil fungus
- Primary illness: lung infection
  - Cough, Fever, Fatigue
- Disseminated illness: spreads to other parts of the body – fatal without treatment
- No known "cure"
- No licensed vaccine available
- Laboratory and provider reportable in AZ



\* F. C. Colvard and C. E. Fabner. Prevalence of sensitivity to coccidioidin, with special reference to specific and nonspecific reactions to coccidioidin and to histoplasmin. Dis. Chest 33:125-60, 1957

## Cocci Epidemiology

Valley Fever in the U.S.\*

- Endemic areas: Southwestern US, Mexico, parts of Central and South America
- 60% of US disease in AZ
- Mode of transmission
  - Inhalation of spores from soil and dust
- Incubation period: 1 to 4 weeks (primary infection)

## Rates of Reported Valley Fever (VF) in Arizona, 1993-2008



\* Valley Fever became lab reportable in 1997

## Coccidioidomycosis Diagnosis

- Tissue diagnosis and culture most specific
- Serology to detect anticoccidioidal antibodies is most sensitive and most used
- Immunodiffusion (ID)
  - Traditional and most studied
  - Very specific, but not sensitive in early disease
- Enzyme immunoassay (EIA)
  - Newer, less expensive and easier to perform
  - Thought to be more sensitive in early disease detection
  - Concern about specificity, especially IgM

## Need & Relevance

- Need
  - Of the estimated 150,000 U. S. cocci infections per year, approximately 60% occur in Arizona, making this state the focal point for investigation of the disease
  - The EIA is the easiest and least expensive to perform, but its sensitivity and specificity can be problematic
  - Early in disease the test can be falsely negative
  - Likewise, false positives may occur, leading to additional diagnostic testing and unwelcome patient anxiety
  - The results from using EIA has not yet been extensively correlated with immunodiffusion

- Relevance
  - Valley Fever grows in desert Southwest soil in low elevations
  - Anyone who lives, visits, or travels in an endemic area may acquire Valley Fever
  - Winds, dust storms, construction and activities that stir up soil cause the spores to become airborne and inhaled
  - People working in construction, landscaping, excavation, agriculture, & archaeology are at increased risk
  - Tourists who are immune-naïve are also at increased risk, especially if engaging in activities that stir up dust

## Research Question

What is the specificity of enzyme immunoassay for coccidioidomycosis diagnosis compared to immunodiffusion?

## Methods

- All Lab Corp coccidioidomycosis serological test results from February 2008 to February 2009 were analyzed and organized
- Calculated sensitivity, specificity, and positive/negative predictive values of EIA IgM and IgG combined
- Gold standard (GS) tests used for comparison included immunodiffusion IgM and IgG (ID), complement fixation titers (CF), and tissue/culture diagnosis
- The GS was considered positive if any GS was positive the day of EIA collection or if tissue/culture diagnosis occurred during the time period
- Cases required EIA IgG and IgM and  $\geq 2$  GS performed the same day for inclusion
- Medical records associated with false positive EIA results were reviewed for coccidioidomycosis symptoms, physician diagnosis, and subsequent positive GS results

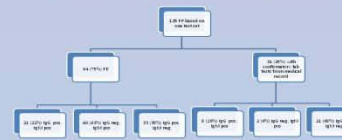
## Results

- 1445 lab test sets met inclusion criteria
  - EIA IgM & IgG with 2 GS tests run on the same date
  - 125 false positives (FP) identified
    - Clinical records requested and reviewed
    - 31 FP  $\rightarrow$  true positive with tissue/culture diagnosis and/or positive GS test reported in clinical record
  - 94 false positives
    - Reported sensitivity, specificity, PPV, NPV at this level

	GS+GS+ (Disease)	GS- (No Disease)
EIA+	150	94
EIA-	29	1172

EIA sensitivity = 83.8%  
 EIA specificity = 92.6%  
 Positive predictive value = 61.5%  
 Negative predictive values = 97.6%

## Summary of "False Positive" EIA Results



## Clinical Review of 94 False Positive Results

- 92/94 (97.9%) were associated with documented coccidioidomycosis symptoms
- 76/94 (80.9%) were associated with documented physician-diagnosed disease

## Summary

- Largest investigation of EIA specificity for coccidioidomycosis diagnosis
- EIA specificity = 93% (PPV 62%) based on laboratory tests alone
- 25% of "false positive" EIA results represent lab confirmed disease
- 23% of "false positive" EIA results are both IgG and IgM positive, increasing the likelihood that they represent true disease

## Conclusions

- $\geq 25\%$  of positive EIA results with negative "gold standard" tests represent true disease
- Single immunodiffusion/complement fixation tests are not a sufficient "gold standard" for coccidioidomycosis diagnosis
- Association of "false positive" EIA results with coccidioidomycosis symptoms and diagnosis suggests clinical correlation may improve EIA diagnostic utility

## Limitations

- Repeat serologic test results occurring after February 2009 were not available possibly leading to missed diagnoses
- Serologic test results were only reviewed from only one laboratory - correlation with other laboratories' results is needed
- Laboratory methods may vary in different laboratories

## Future Directions

- Correlation with other laboratories' results is needed
- Evaluation of the impact of the results within the community
- Recommendations to laboratories about how to report cocci serological testing results

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