

Current Diagnosis of Coccidioidomycosis: Definitive, Presumptive, and Maybe

November 5, 2011

for

Advanced Clinical Aspects of Coccidioidomycosis

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And

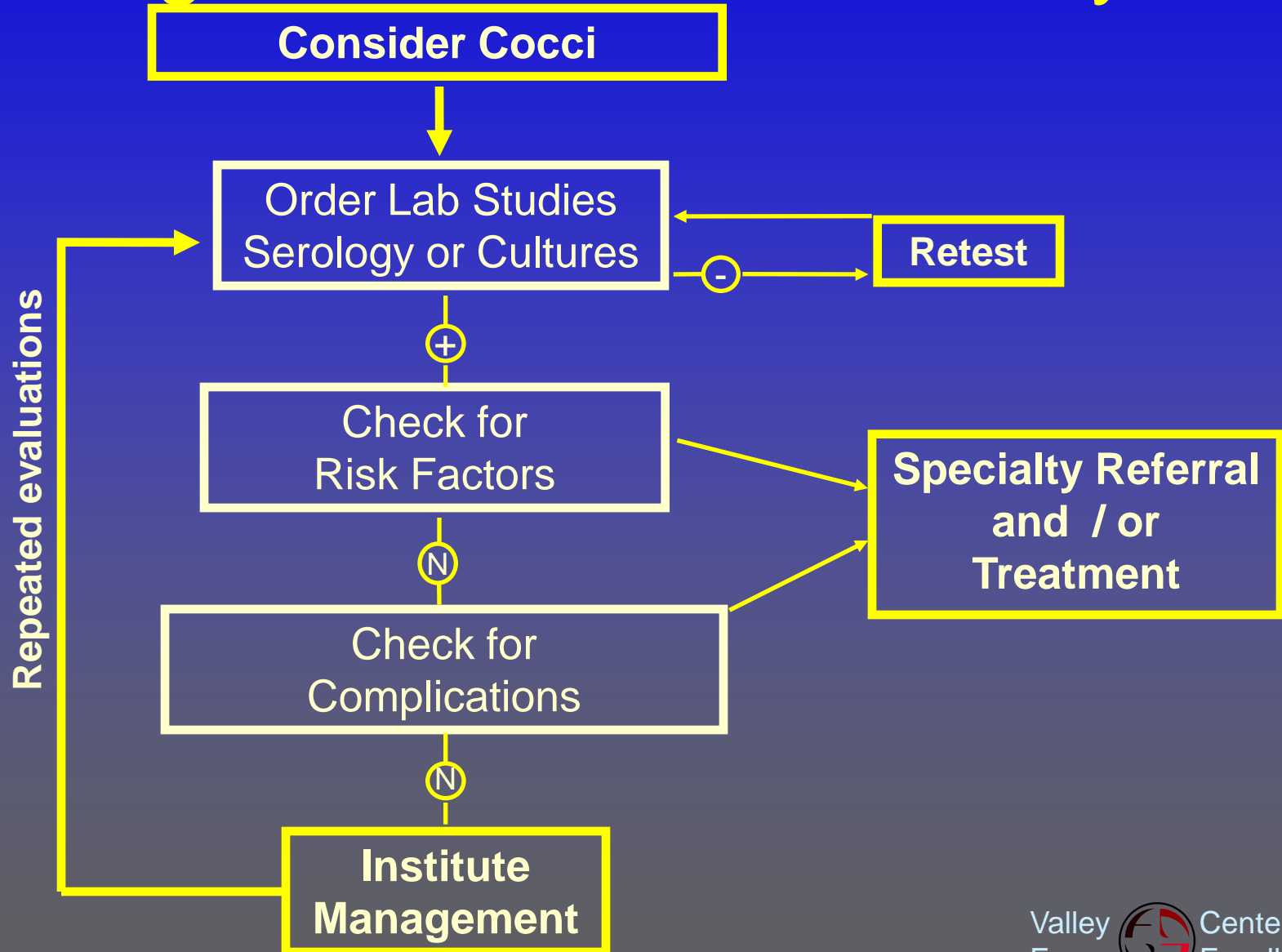
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Disclosure

Dr. John Galgiani is
also
Chief Medical Officer
and
A significant stock-holder
In
Valley Fever Solutions, Inc.

Management of Coccidioidomycosis



When to Consider Valley Fever? Summary

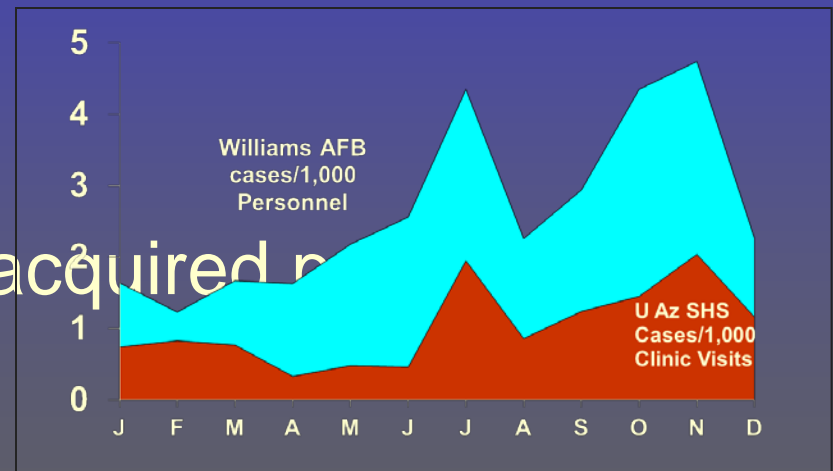
- In Arizona, Valley Fever is very common. It should be in the differential often.
- More frequent between the monsoons and the winter rains.

- Settings:

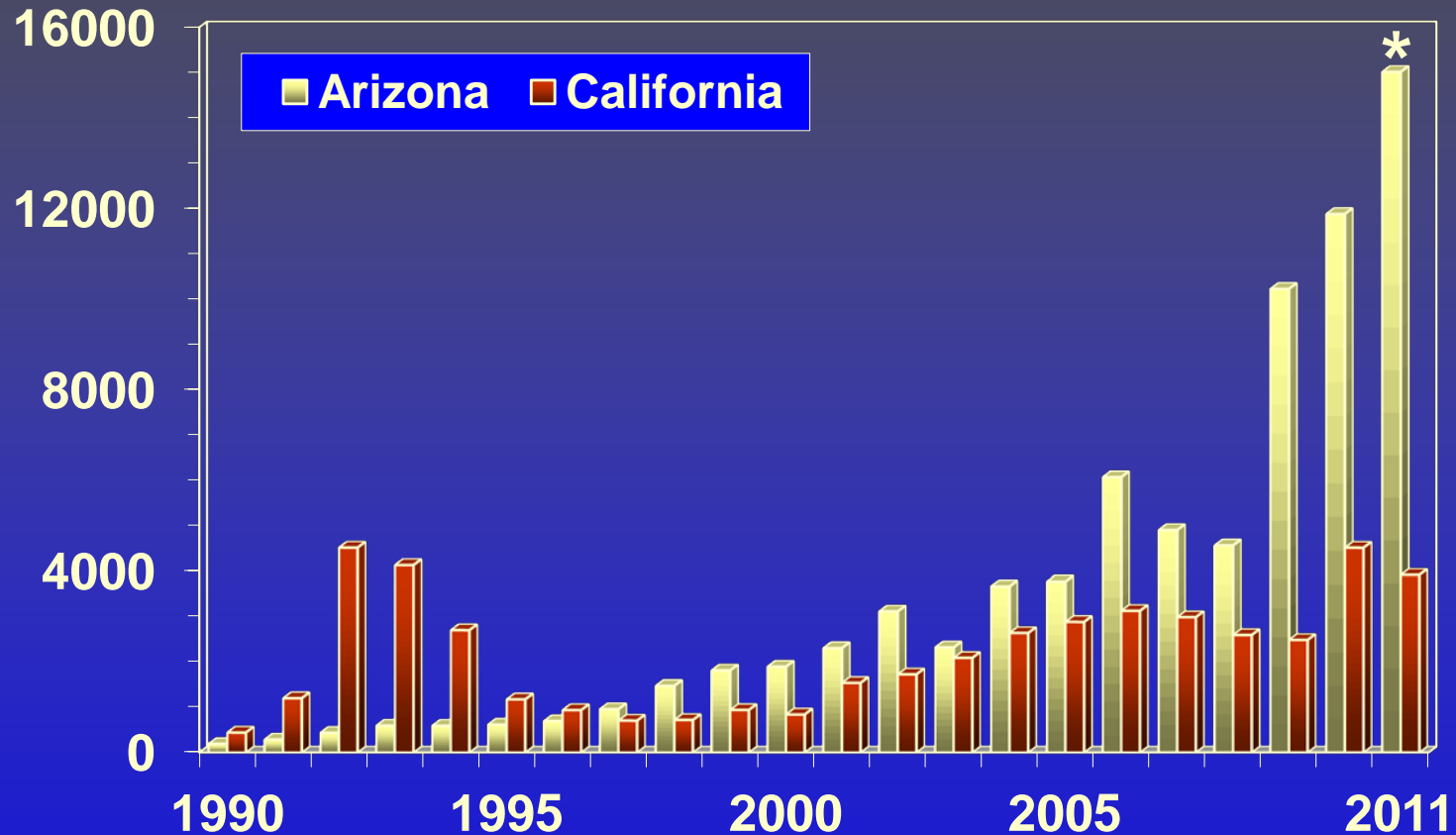
Always in community acquired

Rheumatism.

Rashes.



Reported Valley Fever

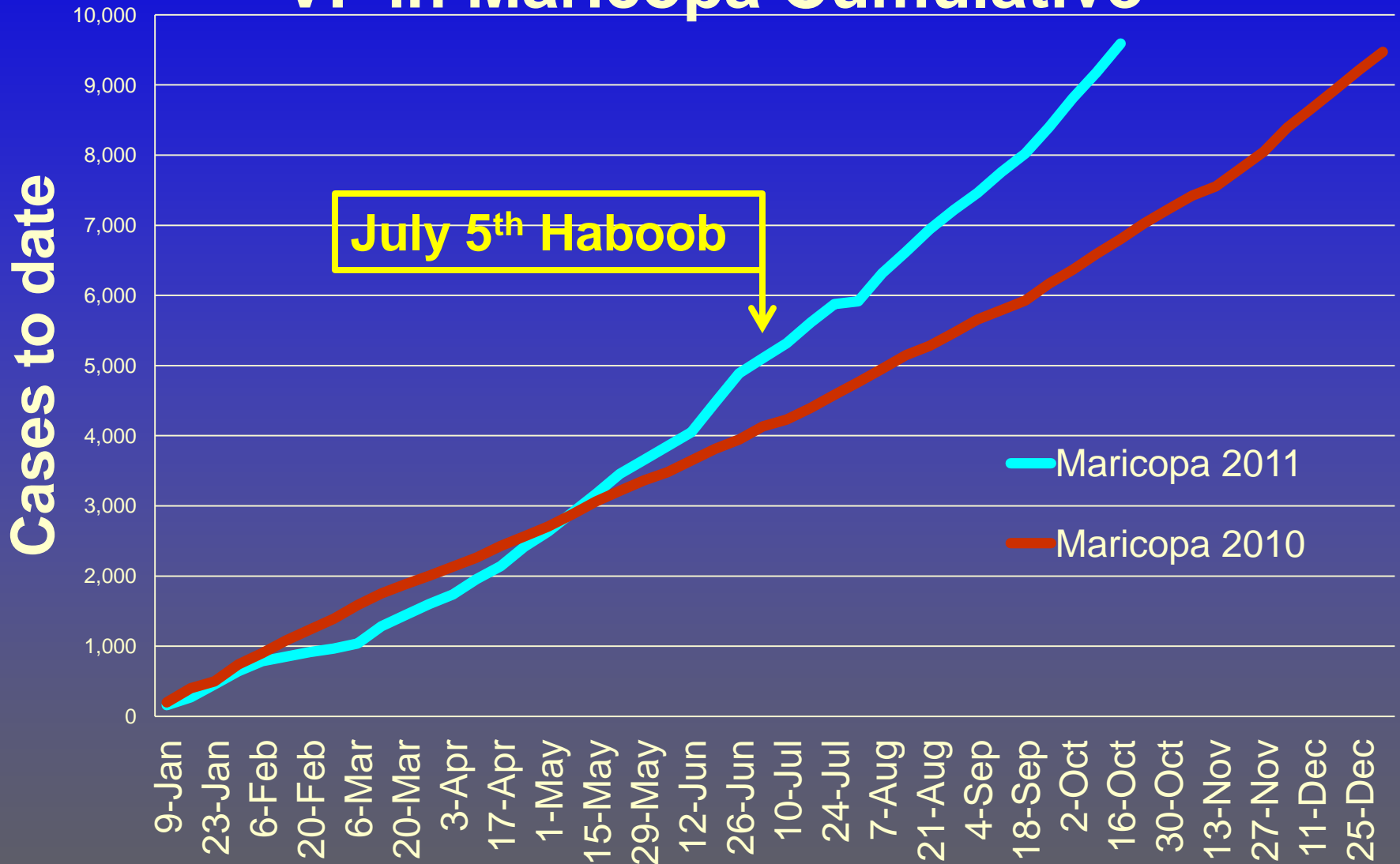


* 2011 extrapolated from week 43 MMWR

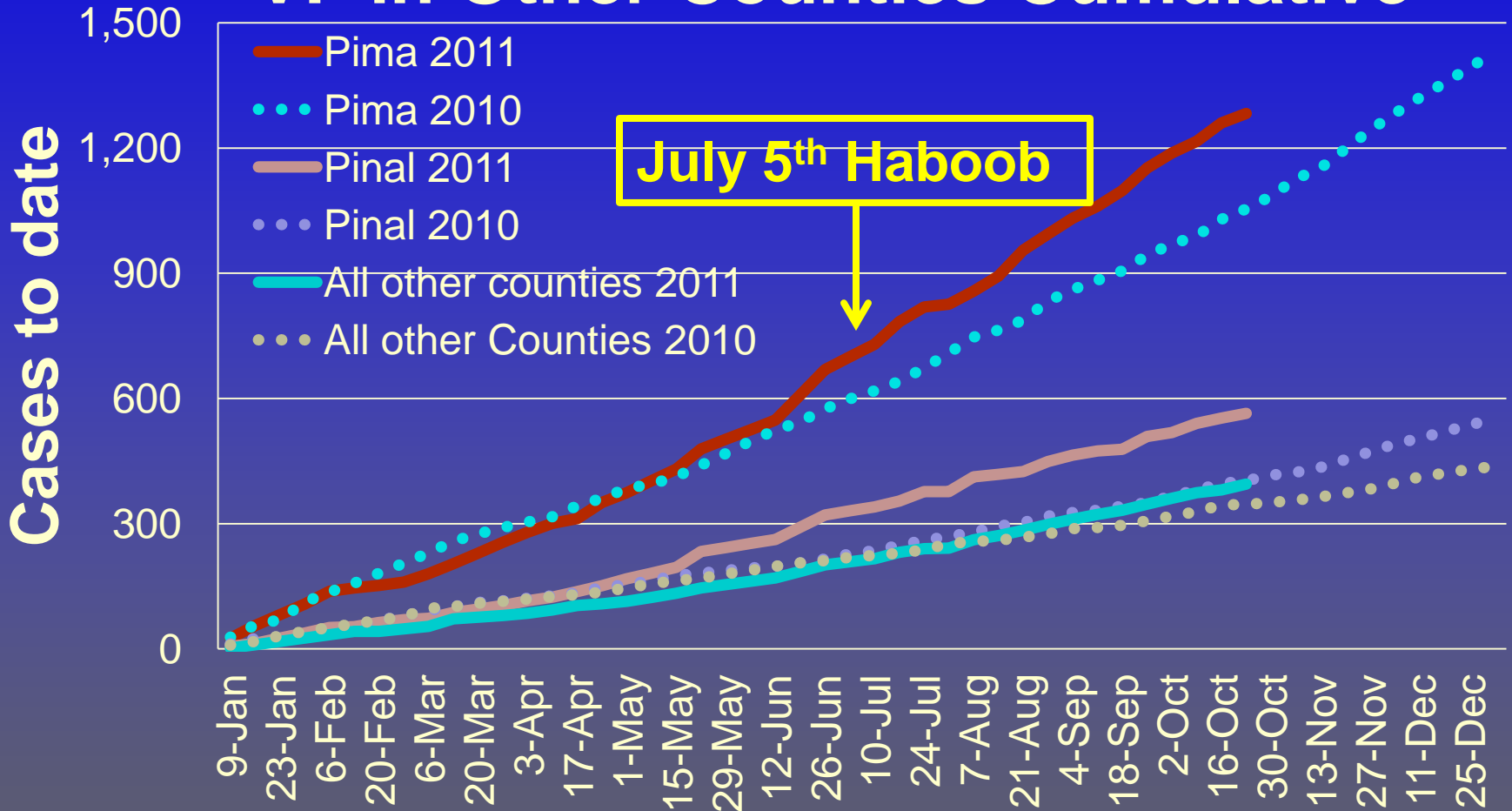
Phoenix, July 5th, 2011



VF in Maricopa Cumulative



VF in Other Counties Cumulative



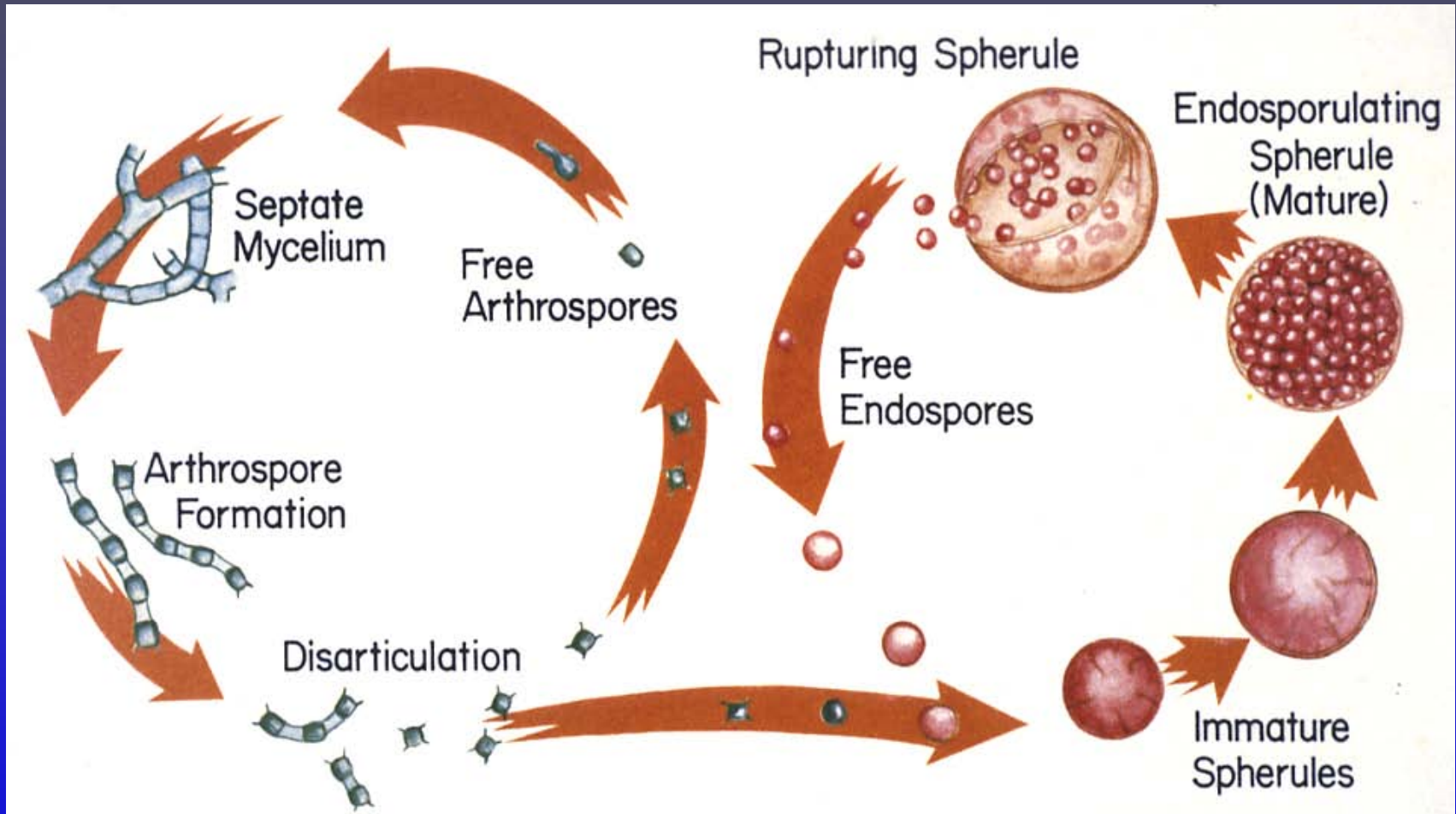
Diagnostic Confidence in Coccidioidomycosis

- How good are the tests?
 - What do we know
 - What's fuzzy.
- How confident do we need to be to optimally manage patients?

Seeing spherules or growing cocci in culture

In the Soil

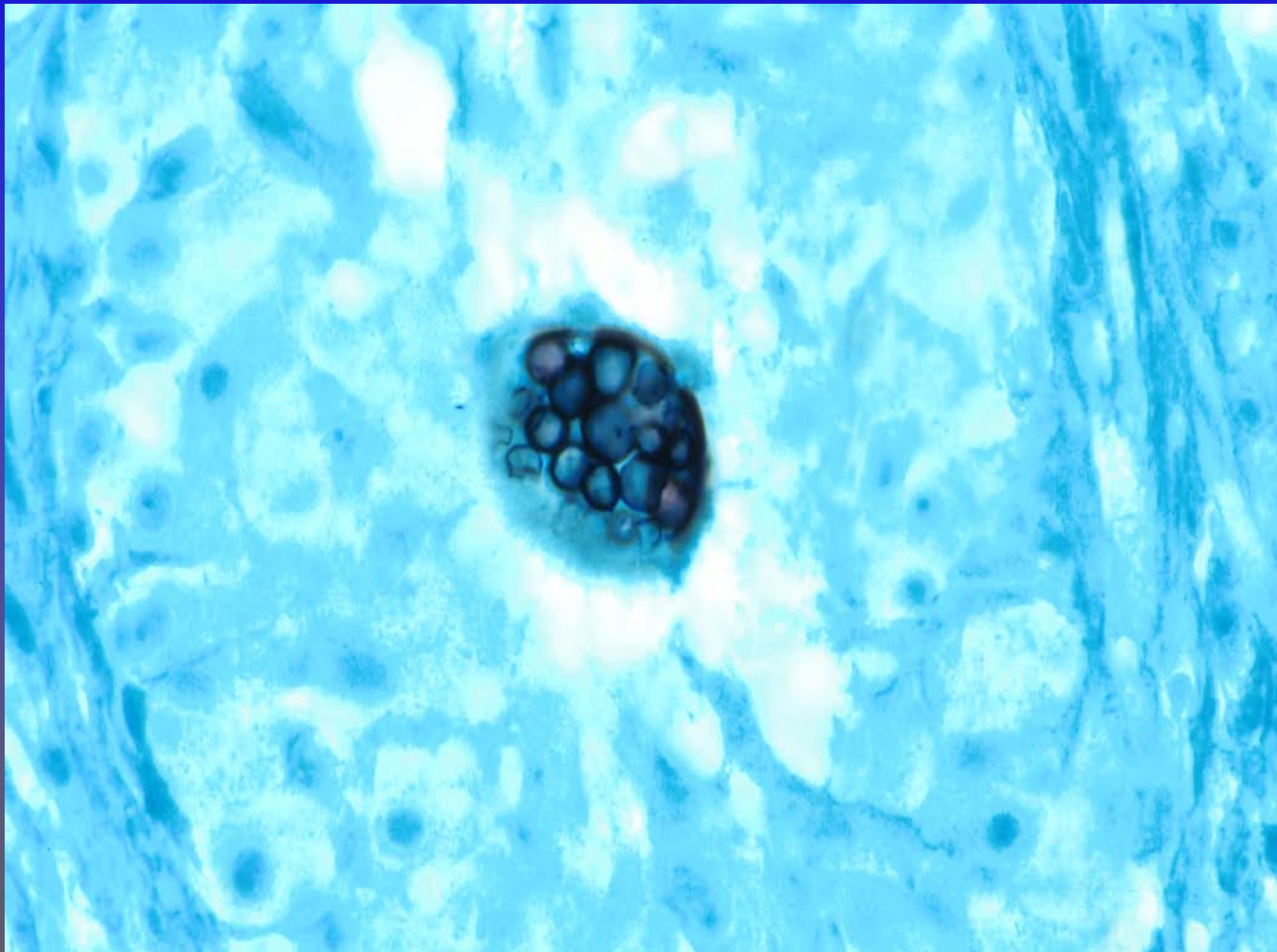
In infected tissue



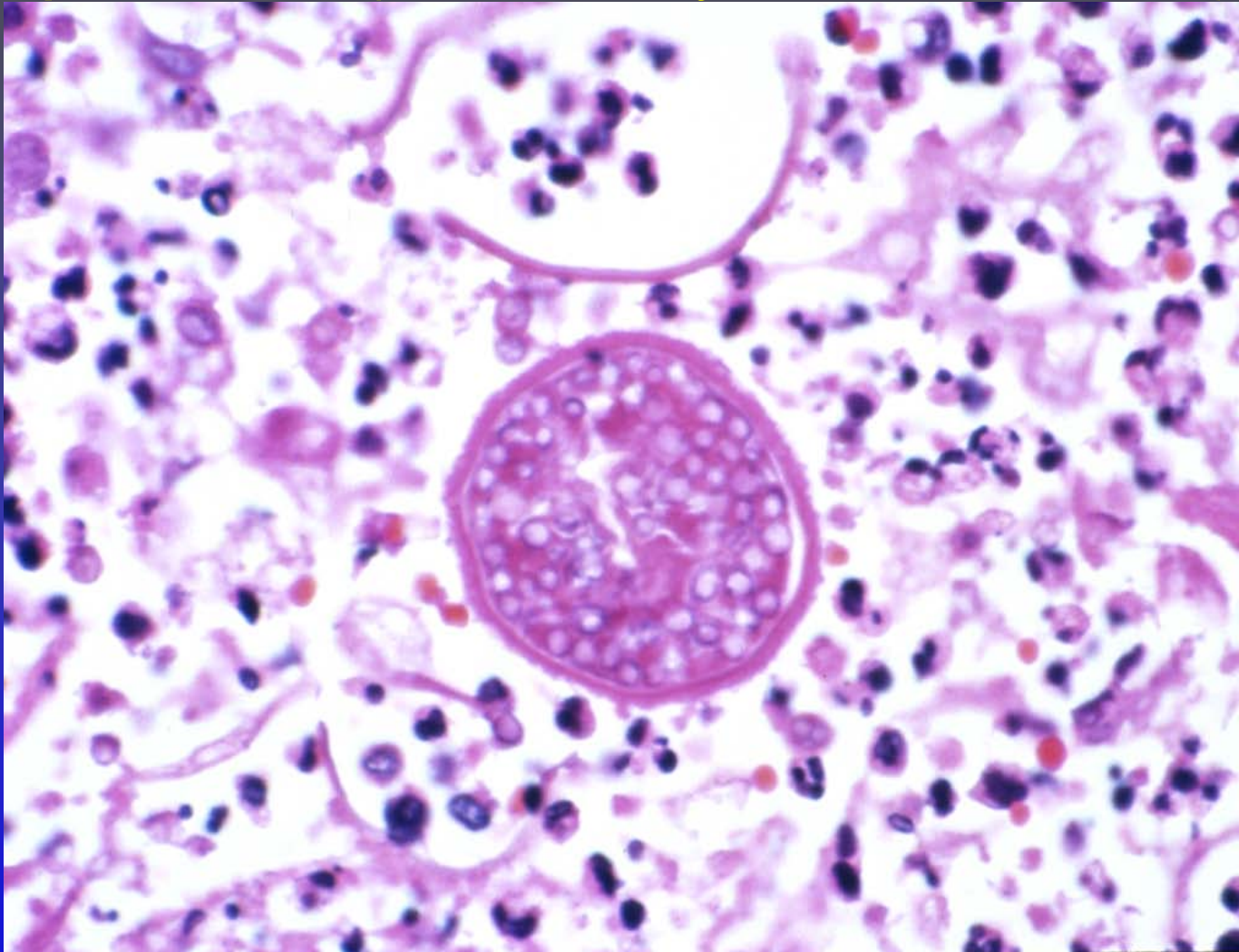
KOH Examination



Spherule (Silver stain of BAL fluid)



Spherules (Hematoxylin-Eosin stain)



Culture of *Coccidioides* spp.

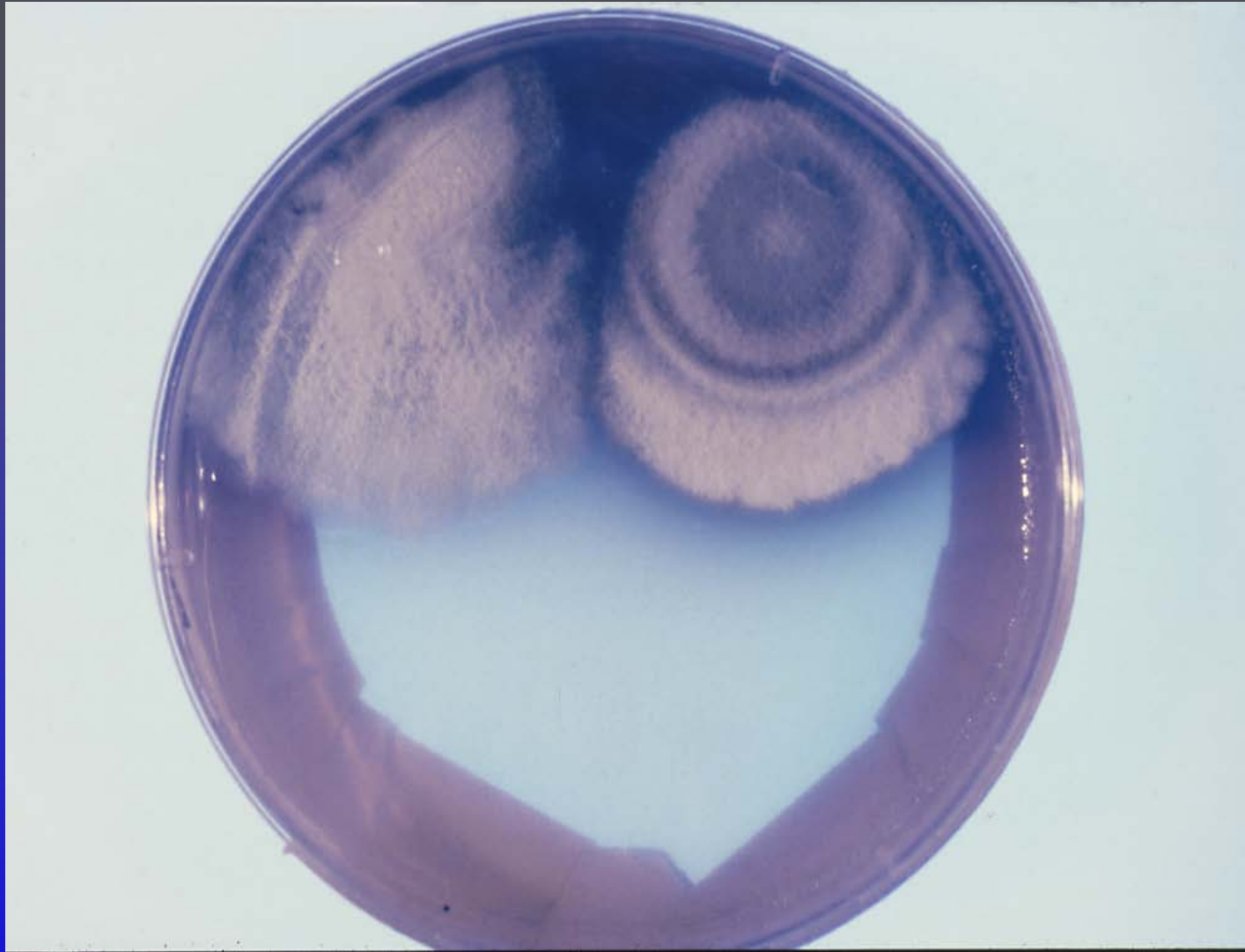
- Primary pneumonia
 - Send patient home with a sputum cup
 - First AM specimen
- Extrapulmonary lesions
 - aspiration of abscesses
 - skin biopsies

Coccy Diagnosis Culture

Growth

- Any medium
- Non-pigmented mold in 3-5 days
- Arthroconidia 1-2 wks





Other tests for Coccidioidomycosis

PCR detection of coccidioidal DNA

- Research publications have demonstrated feasibility
- Some but not all reference laboratories offer PCR for tissue

Coccidioidal antigen detection

- Similar to antigen assay for Histoplasmosis.
- Positive in patients with very extensive disease.
- Send-out to a single reference laboratory.

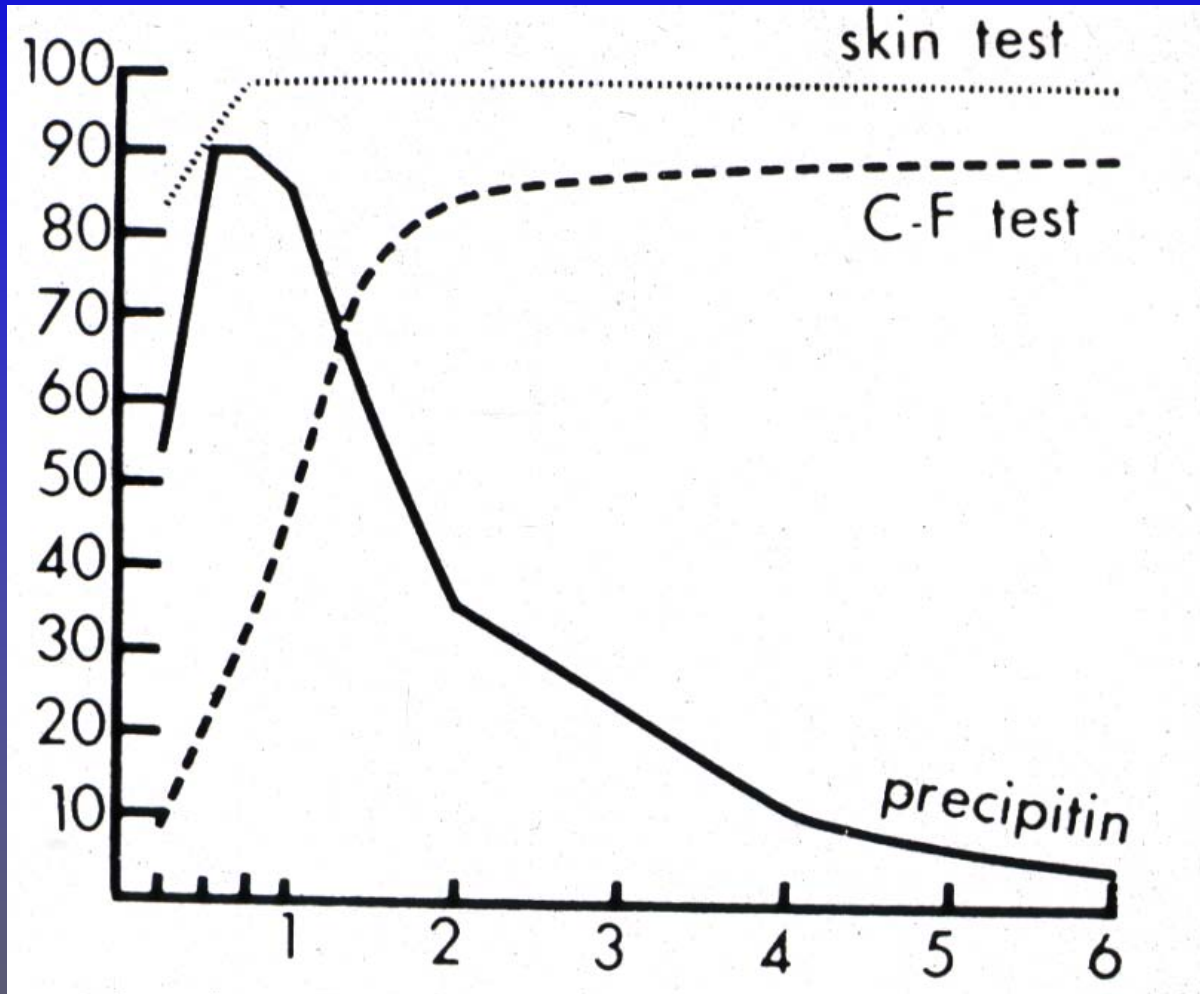
Definitive Diagnosis of Coccidioidomycosis

- Identification of spherules in a clinical specimen.
- Probe-confirmed growth of *Coccidioides* spp.
- PCR positive result on a clinical specimen (?)
- Detection of cocci antigen (?)

Detecting Coccidioidal Antibodies

- Serologic tests are most often used for diagnosis of early coccidioidal pulmonary infections.
- **If coccidioidal antibodies are detected, this is a very specific result and usually important.**
- A negative test does not eliminate the possibility of Valley Fever. Repeated testing improves diagnostic sensitivity.

Percent Positive



Time (months)

Evaluating Incidence of Coccidioidomycosis in the Northwest Valley, Arizona – 2008 Serosurvey Results

Loretta Chang, MD, MPH; Rebecca Sunenshine,
MD; Shoana Anderson, MPH; Sara Imholte, MPH;
Clarisse Tsang, MPH; Sara Santana, MPH; Laura
Erhart MPH; Mare Schumacher, MS; Angela
Ahlquist, MPH; Julie Harris, PhD, MPH; Aleisha
Nesset, DVM; Sanny Chen, PhD; Ken Komatsu,
MPH; **Tom Chiller, MD, MPH**; Ben Park MD



Methods - sampling

- Used remnant sera from major commercial lab
- All sera meeting the following criteria were identified:
 - 65+ years old, living in NWV zip codes
 - 65+ years old, living in non-NWV Maricopa County
- Randomly sampled 800 from each group between Feb - Apr 2009
 - Sample size calculations based on assumed disease prevalence of:
 - 3% in NWV
 - 1.5% in non-NWV

Serosurvey Results

	NWV n (%) (n=797)	Maricopa County n (%) (n=797)	p-value
Positive by ID	9 (1.1%)	6 (0.75%)	0.6
Median age (range)	74 years (65-97)	72 years (65-99)	1.0
Males	383 (49%)	369 (47%)	0.5

Complement fixation (CF) titer levels for Coccidioidomycosis-positive case-patients

CF titer	total
AC 1:4	1
AC 1:8	2
CF 1:2	1
CF 1:8	2
CF 1:16	3
CF 1:32	4
CF 1:128	1

So What About the EIA tests?

Suspected Coccidioidal Pneumonia

n=138, first specimens only

CF or TP Immuno- diffusion Test Results

Negative

Positive

Meridian EIA

Negative

67%

2%

Positive

15%

17%

PRAg2 ELISA

Negative

55%

4%

Positive

27%

14%

Wieden et al. JID May '96

Sensitivity of TP/CF Testing

- EIA and/or ELISA positive
 - 54%
- TP and/or CF positive
 - 18%
- At least 1/3 of EIA only first specimens were corroborated with subsequent TP/CF positives or positive cultures
- Conclusion:

Up to 2/3 of **early** infections detected by newer tests are missed by TP and CF tests.

Specificity of Enzyme Immunoassay for Serologic Coccidioidomycosis Diagnosis Compared to Immunodiffusion

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Disclaimer

The findings and conclusions in this presentation are those of the author(s) and do not necessarily represent the views of the Centers for Disease Control and Prevention or the Arizona Department of Health Services.



Research Objective

- To determine the specificity of enzyme immunoassay for coccidioidomycosis diagnosis
 - Compared to immunodiffusion
 - Based on existing laboratory data reported to public health



Need & Relevance

- 60% of the estimated 150,000 U. S. cocci infections per year make AZ the focal point for investigation
- EIA is the easiest and least expensive diagnostic test to perform, but sensitivity and specificity are not clearly defined
- Early in disease the test can be falsely negative
- False positives may occur, especially EIA IgM, leading to additional diagnostic testing and patient anxiety
- EIA results have not been extensively correlated with immunodiffusion (ID)
- ID is used as a confirmatory test for positive EIA results by some laboratories as recommended by Kaufman et al.



Methods

- All Lab Corp cocci serological test results from February 2008 to February 2009 were requested, organized, and reviewed
- Inclusion criteria: data sets with EIA IgM and IgG and ≥ 2 comparison tests (CT) performed the same day
- Tests used for comparison (CT) included:
 - Immunodiffusion IgM and IgG (ID)
 - Complement fixation titers (CF)
 - Tissue/culture diagnosis
- Calculated sensitivity, specificity, and positive/negative predictive values of EIA IgM and IgG combined
- The CT was considered positive if any CT test was positive the day of EIA collection or if tissue/culture diagnosis occurred during the study time period



Methods Continued

- Requested and reviewed the medical records associated with false positive EIA results for:
 - Coccidioidomycosis symptoms
 - Physician diagnosis
 - Subsequent positive CT test results through December 2010



The Initial Results

1445 lab test sets met inclusion criteria

	CT+ (Disease)	CT- (No Disease)
EIA+	119	125
EIA-	29	1172

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“False
Positives”



“False Positives”

- “False Positive” = EIA positive and CT negative
- Medical records reviewed for 125 “False Positives”
 - 31 (25%) “False Positives” had subsequent positive CT test results in the medical record
 - 31 results were re-classified as “True Positives” leaving 94 “False Positives”
- Calculated sensitivity, specificity, PPV, & NPV

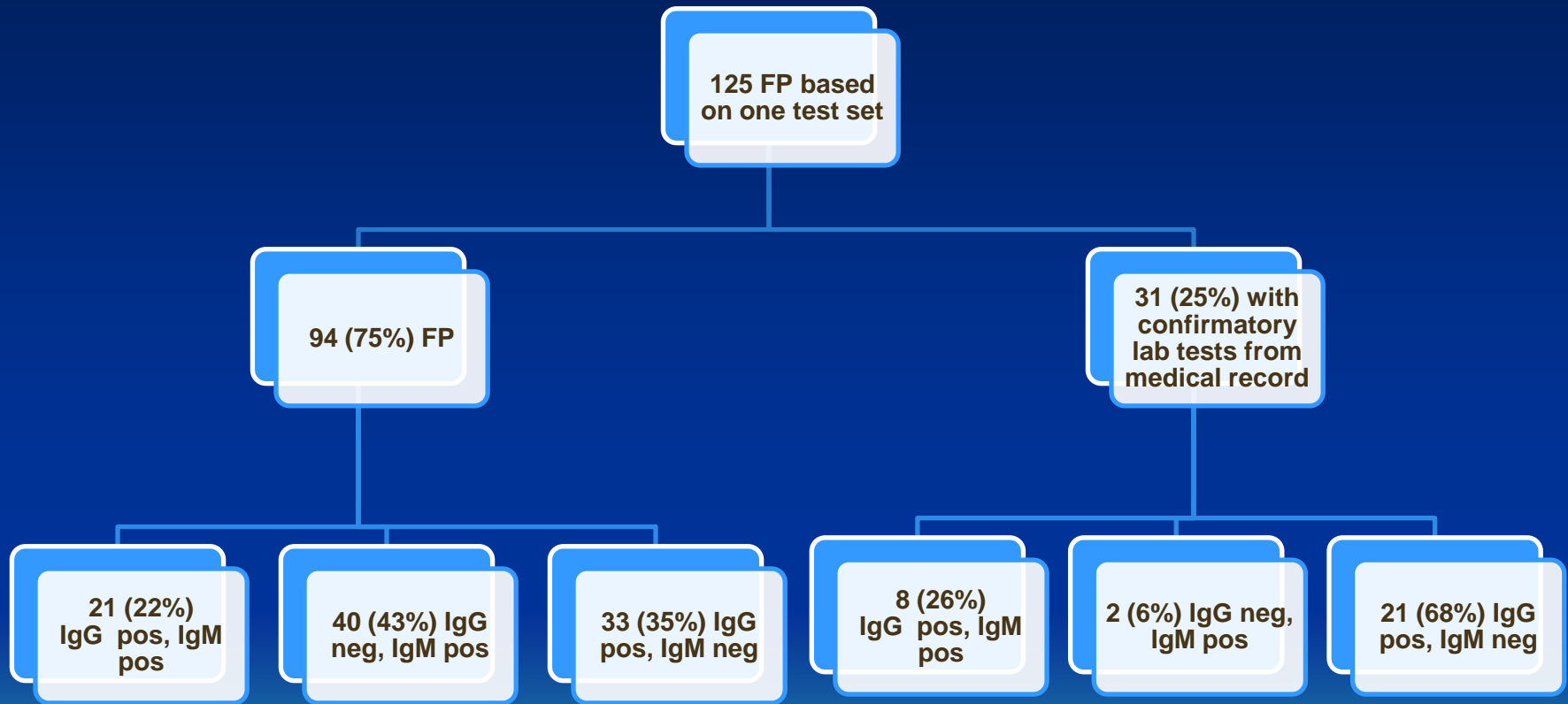


Results (N=1445)

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

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

Summary of “False Positive” EIA Results



54 of 94 (57%) = IgG+

29 of 31 (94%) = IgG +

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

- This is the largest investigation of EIA specificity for coccidioidomycosis diagnosis
- EIA specificity = 93% (PPV 62%) based on laboratory tests alone
- 25% (31/125) of “false positive” EIA results represent lab confirmed disease
- 22% of the remaining 94 “false positive” EIA results are both IgM and IgG positive, increasing the likelihood that they represent true disease
- 57% of all “false positive” EIAs are IgG positive



Limitations

- Repeat serologic test results occurring after December 2010 were not available possibly leading to missed diagnoses
- Serologic test results were reviewed from only one laboratory possibly overlooking tests that would have confirmed disease
- Laboratory methods may vary in different laboratories



Conclusions

- The current practice by some laboratories of confirming all positive EIA results with ID leads to missed coccidioidomycosis diagnoses and an underestimate of disease burden by public health
- Single immunodiffusion/complement fixation tests are not a sufficient “gold standard” for cocci diagnosis
- Association of “false positive” EIA results with coccidioidomycosis symptoms and diagnosis suggests clinical correlation may improve EIA diagnostic utility
- Repeat serologic testing should be considered for “false positive” EIAs



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John Galgiani



Is EIA IgM Specific? Yes

- 405 patients with Meridian EIA tests:
 - Only 28 (7%) showed IgM positive with IgG negative.
- Of the 28:
 - 24 were CF and/or immunodiffusion positive.
 - The other four had either culture or histologic confirmation.

Is EIA IgM Specific? No

- Of 2,139 Meridian EIA tests:
 - Only 104 (5%) showed IgM positive with IgG negative.
- 17 patients with IgM only EIA:
 - Only one was confirmed by immunodiffusion at UC Davis (both IDTP and IDCF)
 - Only three (incl. the UCD +) were clinically judged to have coccidioidomycosis.

What about Isolated IgM Pos?

- They are not particularly common (5-15%)
- Different laboratories have yielded different correlations with “likely cocci.”
- Possible causes include:
 - Patient selection.
 - Manufacturer quality control.
 - Differences in performing the assay (especially stringency of the wash step).

How confident do we need to be to optimally manage patients?

- The sicker the patient, the more certain the diagnostics should be.
 - Culture or Histology is best.
 - At the very least immunodiffusion or CF tests.
- Less acutely ill patients whose serologic tests are indeterminate or negative may be managed without a secure diagnosis.

Thank-you

Valley Fever Center for Excellence



College of Medicine

