Challenges to Developing Drugs and Vaccines for Coccidioidomycois

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NASEM Workshop on Valley Fever

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Valley Fever Center for Excellence

Disclosures

Antifungal drug development

- The University of Arizona is the sponsor of an IND to develop nikkomycin Z as an antifungal drug, and I am responsible for filing the IND amendments.
- From 2007 to 2017 I was Chief Medical Officer for Valley Fever Solutions which licensed nikkomycin Z.

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The opinions expressed in this presentation are my own.

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History of Valley Fever Drug Trials

- Cocci clinical trials started with azole antifungals.
- 1970s: Miconazole
  - Hille Levine et al. identified miconazole as effective treatment of experimental coccidioidomycosis in mice.
  - David Stevens et al published multiple Phase II reports of IV miconazole in patients with progressive cocci infections.
  - Results reported as

    i) Response, **ii**) Partial Response, or **iii**) Non-response.

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  - Miconazole received FDA approval for coccidioidomycosis.

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Scoring System Evaluation Stategy

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- 1988: Ketoconazole 400 vs 800 mg for cocci.
  - Baseline score was zero and points **ADDED** for improvement.
  - Depending on extent of disease, big differences in opportunities for points in different patients.

MSG Refinements to Scoring System

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- Baseline score was all abnormal points and points **SUBSTRACTED** for improvement.
- Response was defined as some fixed percent decrease in abnormality score (i.e., ≥50% decrease in score).
- Critically important details for the scoring system to “work”:
  - Exact abnormalities must be repeated on future evaluations.
  - Unrepeated observations did not change the abnormality score.
  - F/U cultures usually not repeated and was removed from scoring.

NIH-Funded MSG Track Record

Fluconazole, phase II:

- CNS: 50 subjects
- Non-CNS Dissem. & Chronic Pulm.: 75 subjects

Itraconazole, phase II:

- Non-CNS Dissem. & Chronic Pulm.: 47 subjects

Flu vs Itra, phase III:

- Non-CNS Dissem. & Chronic Pulm.: 198 subjects

Posaconazole phase II:

- Non-CNS Dissem. & Chronic Pulm.: 20 subjects

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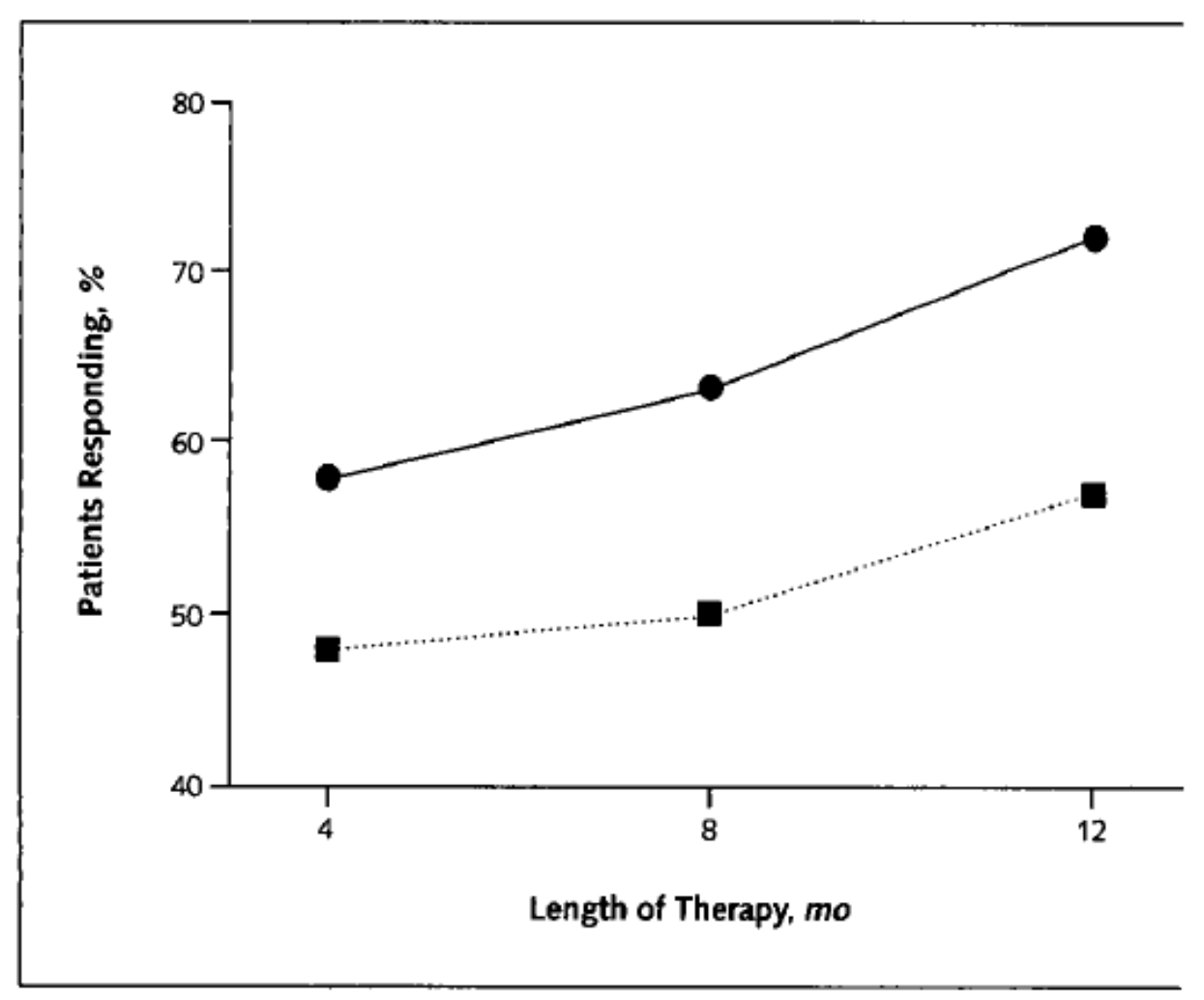
NIH-MSG Flu vs Itra Phase III



Itraconazole

Fluconazole

1º Analysis @ 8 mos: p=0.08

2º Analysis @ 12 mos: p=0.05

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MSG Scoring System

- Pros
  - Quantitative description of the proportion of clinical response following the initiation of therapy.
  - Patients with widely different manifestations could be grouped together on a common scale.
  - Response score generally agreed with investigator's global assessment.
- Cons
  - Results have not been validated. As such, results may not be an allowed end-point by the FDA for a pivotal trial.
  - Exact criteria and methodology for scoring are not agreed upon.
  - Measurements need to be repeated precisely. Does not lend itself to retrospective studies

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- All drugs now used for cocci are off-label treatments.
  - During the NIH-sponsored MSG, many relatively large phase II multi-center trials were completed and published.
  - Since then, newer drugs, such as posaconazole and isovuconazole, have had no such large prospective clinical trials and are nonetheless in use.
  - Thus, by obtaining FDA approval for another indication is the established path for developing new treatments for cocci patients at present.

Medicare Outpatient 2020*

State	Population >65 yrs (1,000s)	Fluconazole		Posaconazole		Isavuconazole	
		Days	Cost	Days	Cost	Days	Cost
AZ	1,309	1,229 K	$2.5 M	27.7 K	$4.33 M	14.4 K	$2.65 M
CO NM	1,264	201 K	0.2 M	2.9 K	.40 M	0.2 K	0.89 M
UT	383	180 K	0.2 M			0.4 K	0.08 M
NV	512	106 K	0.1 M	0.5 K	.08 M		

*Data.cms.gov

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- Need FDA-approved end-points for disseminated and chronic pulmonary infections.
  - Validated scoring system?
  - Patient reported outcomes?
- Need an appropriate comparator drug.
- Since there is no FDA-approved treatment, non-inferiority designs are not possible.

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- Many symptoms are immunologic responses triggered by infection and the effect of antifungals on their resolution is uncertain.*

*Galgiani et al. 5/1/2020. CID

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- Only feasible endpoint is reduction in length of illness; Preventing complications would require prohibitive N.
- Many symptoms are immunologic responses triggerd by infection and the effect of antifungals on their resolution is uncertain.
- Since cocci is frequently diagnosed late, opportunity to determine a therapeutic effect might be missed.

Rational for a Valley Fever Vaccine

- Patients after infection are presumed to have life-long immunity.
- Southwest residents and tourists
  - Prevent ~50,000 primary illnesses/yr
  - Prevent ~750 disseminated infections/yr
  - Reduce $1.5 Billion impact*

* Wilson et al. 2019
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  - Prevent antibiotic use (4 antibiotic orders per Valley fever patient before correct diagnosis**)

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**Donovan et al. 2019

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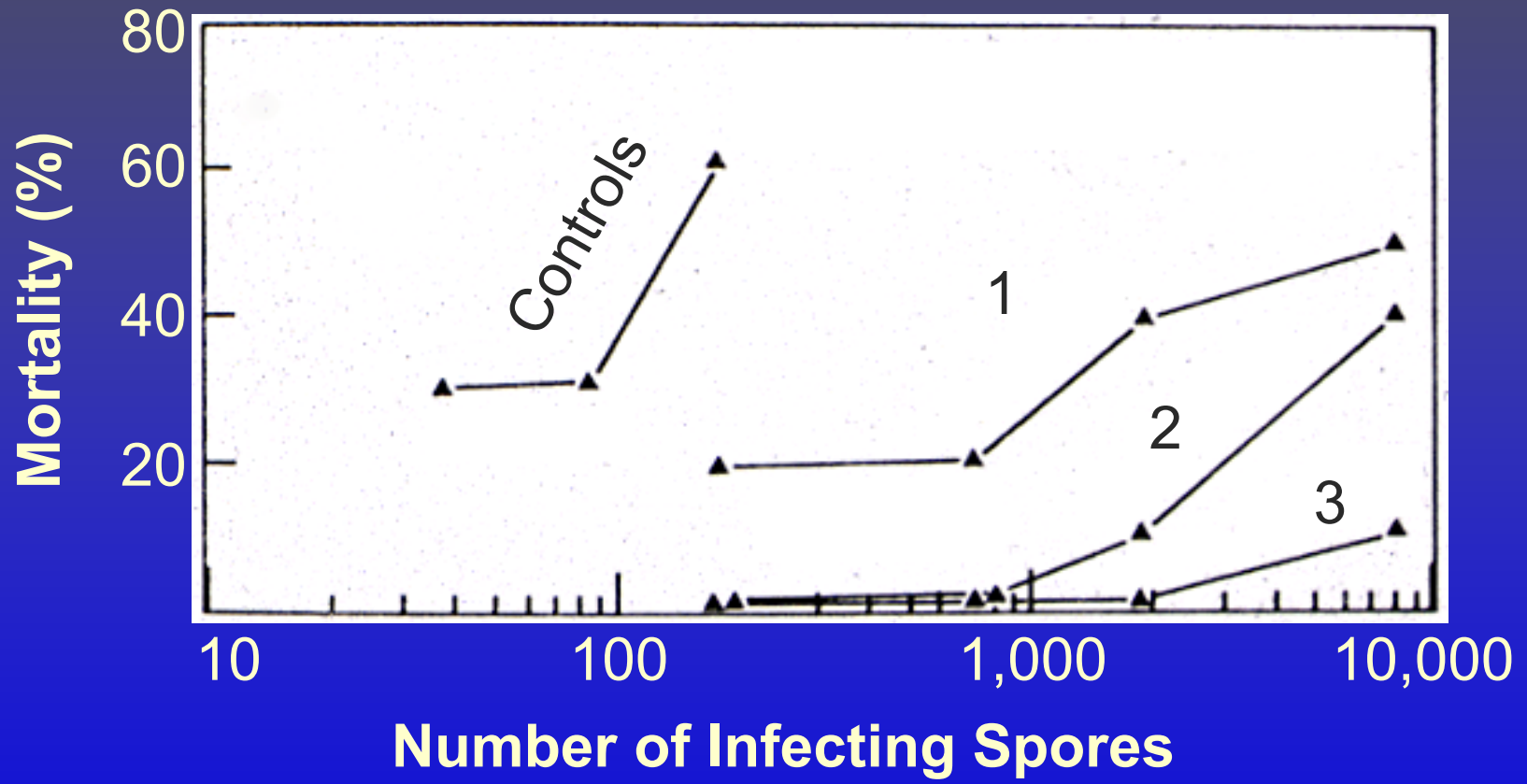
Whole Formalin-Killed Spherule (FKS) Vaccine Protection of Mice* 1, 2, or 3 doses (0.8 mg/dose)



*J Immunol, 1965

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FKS Vaccine Trial Design

- 1980-1985: Any endemic adult resident with four negative cocci skin tests.
  - Excluded 52% and 39% of volunteers in Bakersfield and Tucson, respectively.
- Coccidioidal serologies at periodic follow-up and for clinical illness.
- 3,242 and 3,234 person-years for vaccine and placebo subjects, respectively.

Injection-Site Inflammation
Formalin-killed Spherule Vaccine

	Self-Reported Reactions	
	Vaccine	Placebo
Total enrollment	1344	1362
None	5.6%	89.1%
Mild	56.6%	10.0%
Moderate	32.9%	0.8%
Marked	4.5%	0.1%
Unacceptable	0.4%	0.0%

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Humans received whole cell Vaccine (1.4 mg x 3 doses)

Group	n	New Valley Fever Infections	
		Definite	Possible
FKS	1,436	9	9
Placebo	1,431	12	13

Conclusion: Whole formalin-killed spherules (FKS) were not effective in preventing human Valley Fever.

*Am Rev Respir Dis, 1993

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Hypothetical Clinical Trial Results
1500 subjects per group
If Placebo Group had 15 cases

Vaccine Group Case #	Percent Effectiveness	χ^2 p value	95% Confidence
4	74%	0.02	33% - 95%
3	80%	0.01	43% - 100%
2	87%	0.004	57% - 100%
1	93%	0.001	73% - 100%

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Challenges for doing RCTs Valley Fever Vaccines

- Population to study
  - High risk or all with endemic risk?
  - Should subjects with prior infection be excluded?
  - If so, how?
    - Spherusol (40% false negatives*)
    - *In vitro* PBMC-stimulation
    - In-tube TB-like IGRA for cocci?
- Endpoints
  - Any evidence of infection?
    - Skin test, PBMC stim. Conversion
    - Serologic conversion
  - Any symptomatic infections?
    - Markers of inflammation
    - Patient reported outcomes
  - Only severe illnesses, chronic pulmonary or disseminated?

*Lucas et al, CSG 2017

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Thank-You

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