Valley Fever Institute at Kern Medical

Coccidioidal Immunization: Past, Present & Future

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November 18, 2022

Disclosures

The Valley Fever Institute at Kern Medical has identified a financial relationship with:

- ✓ F2G Pharmaceuticals
- ✓ Mycotic Disease Branch, Centers for Disease Control and Prevention
- ✓ Occupational Safety and Health Administration, U.S. Department of Labor

Overview of Coccidioidal Vaccines

- ✓Where we have been
- ✓Where we are
- ✓Where we are going

Coccidioidal Immunization

Curing is Costly,

Prevention is Priceless

The Vaccine Enterprise

Smallpox	Typhoid	Yellow Fever
Rabies	Haemophilus	Dengue
Diphtheria	Pneumococcus	Tuberculosis
Tetanus	Meningococcus	Malaria
Pertussis	Rotavirus	Anthrax
Measles	Varicella/Zoster	Cholera
Mumps	Hepatitis A	Plague
Rubella	Hepatitis B	Japanese Encephalitis
Influenza	Human Papilloma Virus	SARS-CoV-2
Polio		

Coccidioidal Immunization

Average Age at Death (USA)

Year	Age
1900	49
1935	60
1960	70
2019	79

Reasons

- ✓ Air
- ✓ Water
- ✓ Food
- ✓ **Immunizations**
- ✓ Sewage
- ✓ Poverty
- ✓ Tuberculosis

Coccidioidal Immunization

- ✓1895: Dog skin inoculation – Rixford[1]
- ✓1935: "Second infections rare if ever" – Smith[2]
- ✓1961: 7000 cases no second case – Smith[3]
- ✓1999: 20,000 cases one second infection (compromised host CLL) – Pappagianis[4]

1. Rixford E, Gilchrist TC. Two cases of protozoan (coccidioidal) infection of the skin and other organs, Johns Hopkins Hosp Rep, 1896, vol. 10 (pg. 209-68)
2. Smith CE. Epidemiology of acute coccidioidomycosis with erythema nodosum ("San Joaquin" or "Valley Fever"), Am J Publ Health, 1940, vol. 30 (pg. 600-11)
3. Smith, C. E., Pappagianis, D., Levine, H. B., and Saito, M. I. 1961. Human coccidioidomycosis. Bacteriol. Rev. 25: 310–320.
4. Pappagianis D. Coccidioides immitis antigen. J Infect Dis. 1999 Jul;180(1):243-4. doi: 10.1086/314835. PMID: 10353891.

Coccidioidal Immunization

Vaccines:

- ✓Nonviable
  - Epitope Based
  - Nucleic Acid Based
- ✓Viable Attenuated

Coccidioidal Immunization

Mice: Phase 1

✓Freidman & Smith 1956

- Formaldehyde inactivated arthroconidia
- IP → protection but infection

✓Levine et al. 1960, 1965

- Formaldehyde killed whole spherules
- intranasal challenge

Coccidioidal Immunization

Human: Phase 2

Levine & Smith 1967[1]

- Formaldehyde killed whole spherules

Pappagianis & Williams 1984[2]

- Silveira Whole Spherule Vaccine (Vaccine 1)
- Dosing/tolerability

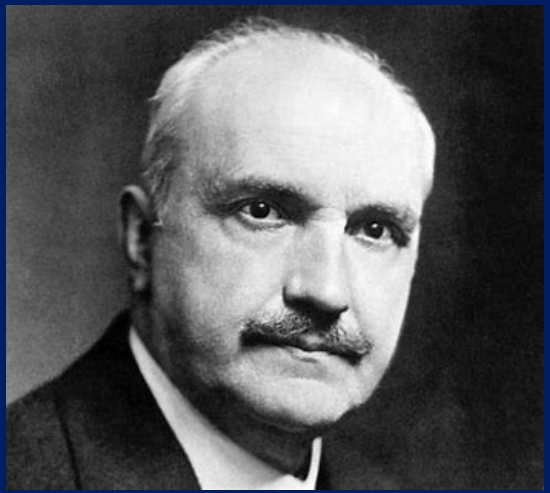
1. LEVINE HB, KONG YC, SMITH C. IMMUNIZATION OF MICE TO COCCIDIOIDES IMMITIS: DOSE, REGIMEN AND SPHERULATION STAGE OF KILLED SPHERULE VACCINES. J Immunol. 1965 Jan;94:132-42. PMID: 14253511.

2. Williams PL, Sable DL, Sorgen SP, Pappagianis D, Levine HB, Brodine SK, Brown BW, Grumet FC, Stevens DA. Immunologic responsiveness and safety associated with the Coccidioides immitis spherule vaccine in volunteers of white, black, and Filipino ancestry. Am J Epidemiol. 1984 Apr;119(4):591-602. doi: 10.1093/oxfordjournals.aje.a113776. PMID: 6424435.

Coccidioidal Immunization

"Those who forget history are doomed to repeat it."

- George Santayana



Coccidioidal Vaccine 1

Human: Phase 3 1980 - 1986

Hans Einstein 1979 meeting

- ✓Einstein
- ✓Larwood
- ✓Cunningham
- ✓Holman
- ✓Anderson
- ✓Johnson

Vaccine 1 - Human Phase 3

✓ Double Blind Randomized Controlled Trial

Pappagianis D. Evaluation of the protective efficacy of the killed Coccidioides immitis spherule vaccine in humans. The Valley Fever Vaccine Study Group. *Am Rev Respir Dis*. 1993;148(3):656-660. doi:10.1164/ajrccm/148.3.656

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TABLE 2

DEMOGRAPHIC CHARACTERISTICS OF PARTICIPANTS

	Vaccine		Placebo	
	(*n*)	(%)	(*n*)	(%)
Ethnic ancestry				
Caucasian	1,247	86.8	1,238	86.5
Mexican-American	73	5.1	70	4.9
Filipino	35	2.4	27	1.9
African-American	26	1.8	39	2.7
Native American	20	1.4	17	1.2
Others	35	2.4	40	2.8
Total	1,436		1,431	
Sex				
Male	657	45.8	623	43.5
Female	779	54.2	808	56.5
Total	1,436*		1,431*	
Occupation				
Outdoor	487	34	484	34
Indoor	946	66	946	66
Total	1,433*		1,430*	
Years in endemic area				
1	121	10.5	116	10.1
1–10	321	28.0	325	28.2
11–20	233	20.3	200	17.4
21–30	250	21.8	269	23.4
31–40	149	13.0	163	14.2
41–50	62	5.4	63	5.5
51–60	11	1.0	15	1.3
Total	1,147		1,151	

* The disparity in these numbers was due to absence of information from 3 and 1, respectively, in vaccine and placebo groups.

Pappagianis D. Evaluation of the protective efficacy of the killed Coccidioides immitis spherule vaccine in humans. The Valley Fever Vaccine Study Group. *Am Rev Respir Dis*. 1993;148(3):656-660. doi:10.1164/ajrccm/148.3.656

Coccidioidal Immunization

TABLE 1

SUMMARY OF COCCIDIOIDAL VACCINE STUDY 1980–1985

	Study Sites				
	B	L	V	NAS-L	T
Enrolled: 2,867	1,294	63	292	503	715
Vaccine: 1,436	650	33	146	252	355
Placebo: 1,431	644	30	146	251	360
Cases: 21					
Vaccine: 9	3	1		2	3
Placebo: 12	6				6
Suspected cases: 22					
Vaccine: 9	3				6
Placebo: 13	6			1	6

Definition of abbreviations: B = Bakersfield; L = Lemoore; V = Visalia; NAS-L = Naval Air Station-Lemoore; T = Tucson.

Pappagianis D. Evaluation of the protective efficacy of the killed Coccidioides immitis spherule vaccine in humans. The Valley Fever Vaccine Study Group. *Am Rev Respir Dis*. 1993;148(3):656-660. doi:10.1164/ajrccm/148.3.656

Cocci Vaccine 1: Reasons for Failure

- ✓Skin testing as marker of prior infection/immunity
- ✓No surrogate marker of Immune Response
- ✓Sample Size Calculation
- ✓Sample Composition
- ✓Infection vs Disease
- ✓Pneumonia End Point (vs, animal models)
- ✓3 doses of vaccine
- ✓Tolerability
- ✓Finance

Pappagianis D. Evaluation of the protective efficacy of the killed Coccidioides immitis spherule vaccine in humans. The Valley Fever Vaccine Study Group. *Am Rev Respir Dis*. 1993;148(3):656-660. doi:10.1164/ajrccm/148.3.656

Cocci Vaccine 1

Conclusion

- ✓Major reason for failure - dose restriction due to toxicity (1/1000 of mouse dose)
- ✓Enrollment too small (& wrong population)
- ✓Predicted cases 10x greater
- ✓Pneumonia as end point

Pappagianis D. Evaluation of the protective efficacy of the killed Coccidioides immitis spherule vaccine in humans. The Valley Fever Vaccine Study Group. *Am Rev Respir Dis*. 1993;148(3):656-660. doi:10.1164/ajrccm/148.3.656

Infection vs Disease

60% Inhaled Valley Fever Spore & Have No Symptoms

40% Inhaled Valley Fever Spore & Have Flu Resembling Pneumonia Illness

10% Inhaled Valley Fever Spore & Have Diagnosed Valley Fever

1% Inhaled Valley Fever Spore & Have Severe Pulmonary Infection or Disseminated Cocci

Coccidioidal Immunization

- ✓The Valley Fever Vaccine Collaborative
- ✓California Healthcare Foundation
- ✓California State University Bakersfield Foundation

Post Vaccine 1

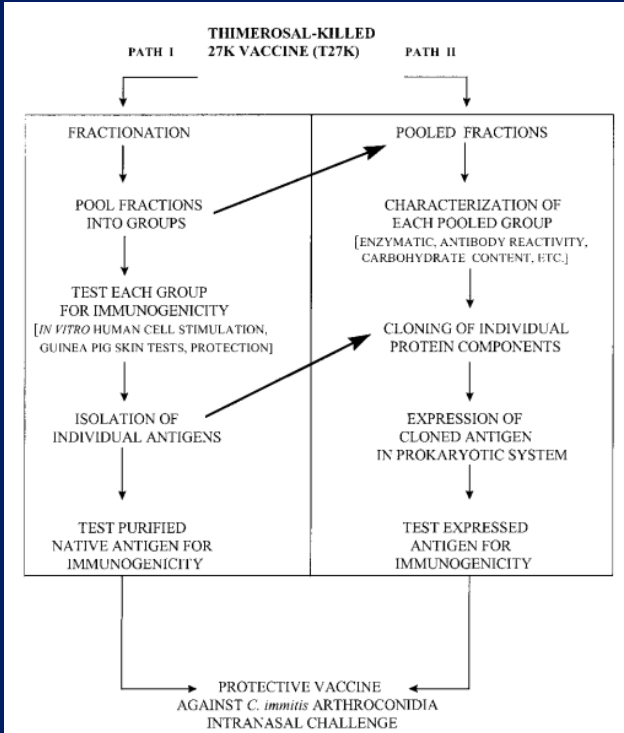

FIG. 1. Preparation of a coccidioidal vaccine. Recovery of immunogenic component(s) from thimerosal-killed 27K vaccine (T27K).

Pappagianis D. Seeking a vaccine against Coccidioides immitis and serologic studies: expectations and realities. *Fungal Genet Biol*. 2001;32(1):1-9. doi:10.1006/fgbi.2000.1243

Coccidioidal Immunization

Table 1. Vaccine antigens.

Antigen	Form	Adjuvant	Activity	Reference
Live attenuated mutants	N/A [a]	N/A	Active	[30,31]
Formalin-killed spherules	N/A	N/A	Active in mice but not humans	[28,32]
Spherule extract	N/A	Various	Active	[29]
Ag2/PRA	Protein, DNA	Various	Moderately active Inactive	[10,33]
β-glucanosyltransferase	Protein	CpG-ODN [b]	Moderately active	[34]
Calnexin	Protein	Glucan and Adjuplex	Modestly active	[35]
Aspartyl protease	Protein	CpG-ODN	Moderately active	[36]
CSA [c]	Protein	CpG-ODN and MPLA [d]	Modestly active	[37]
Ag2/PRA and CSA fusion protein	Protein	CpG-ODN and MPLA	Highly active	[37]
Phospholipase, α-mannosidase and aspartyl protease	Protein	CpG-ODN	Highly active	[36,38]

[a] Not applicable; [b] cytosine triphosphate deoxynucleotide—guanine triphosphate deoxynucleotide immunostimulatory polymer; [c] Coccidioides specific antigen; [d] monophosphoryl lipid A.

Kirkland, Theo N. "The Quest for a Vaccine Against Coccidioidomycosis: A Neglected Disease of the Americas." *Journal of fungi (Basel, Switzerland)* vol. 2,4 34. 16 Dec. 2016, doi:10.3390/jof2040034

Coccidioidal Immunization

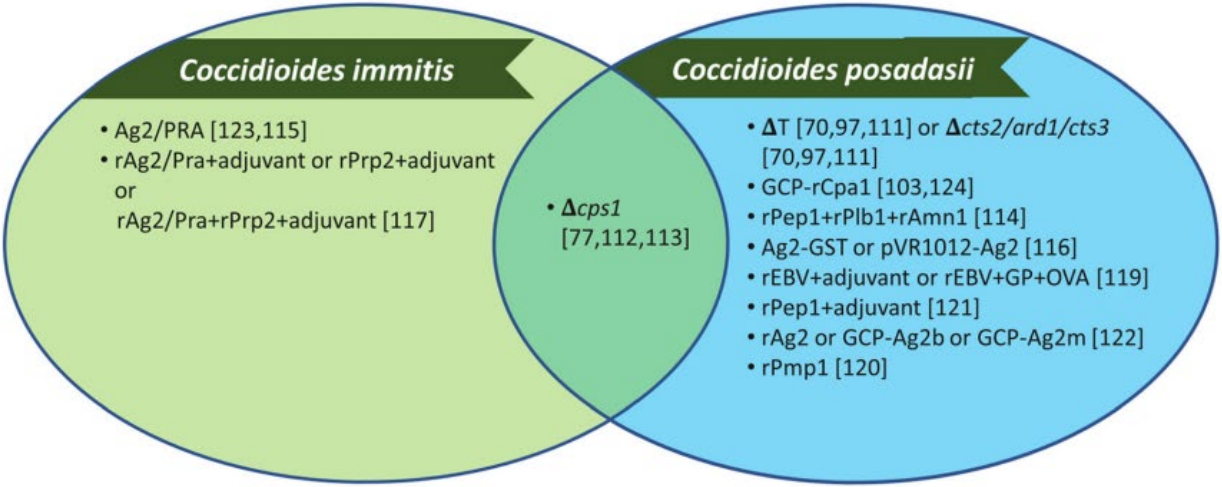

Figure 2. Species tested with coccidioidomycosis vaccine candidates. Vaccination studies against coccidioidomycosis mainly test against *C. posadasii* infections.

Gorris ME, Caballero Van Dyke MC, Carey A, Hamm PS, Mead HL, Uehling JK. A Review of *Coccidioides* Research, Outstanding Questions in the Field, and Contributions by Women Scientists. *Curr Clin Microbiol Rep*. 2021;8(3):114-128. doi:10.1007/s40588-021-00173-9

Coccidioidal Immunization

Problems: Animal Data

- ✓Dose response
  - ➢No PRO in mice
- ✓Intraperitoneal vs Intranasal
- ✓Pneumonic Disease in "successful" immunizations
- ✓Immune status of animal (different mice & different dogs)

Coccidioidal Immunization

Considerations for Future Phase III Trials

- ✓Sample size calculations
- ✓Measurement of prior immunity
- ✓Sample recruitment & retention

Coccidioidal Immunization

"Success is not final, failure is not fatal: it is the courage to continue that counts."

- Winston Churchill