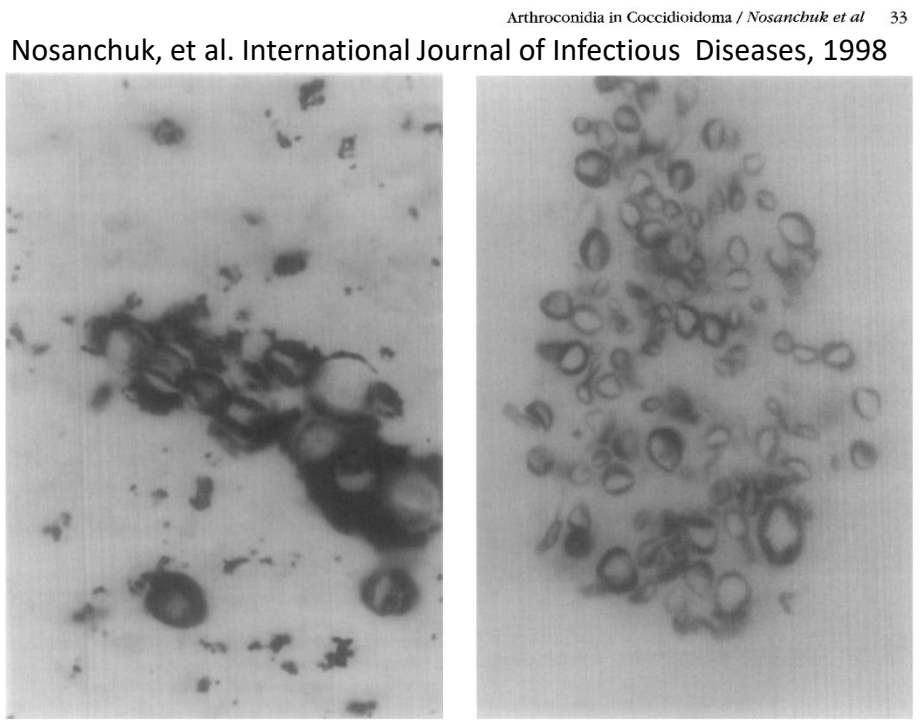
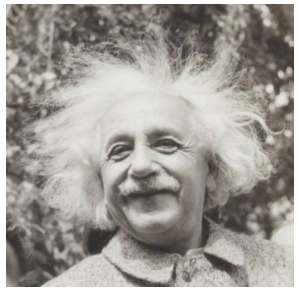


Nosanchuk, et al. International Journal of Infectious Diseases, 1998

Overview of Valley Fever: *why now?*



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Disclosures

- **Funding:**
  - NIH RO1 AI171093
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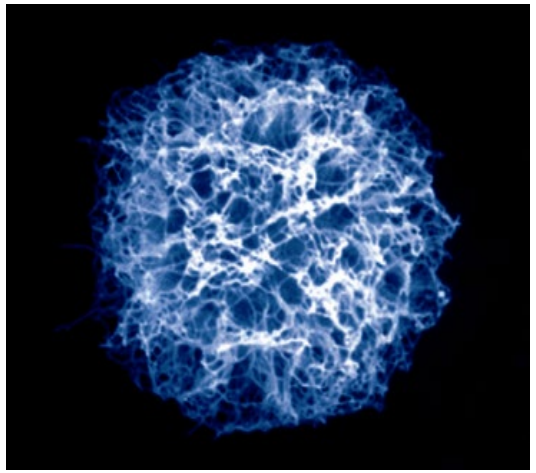
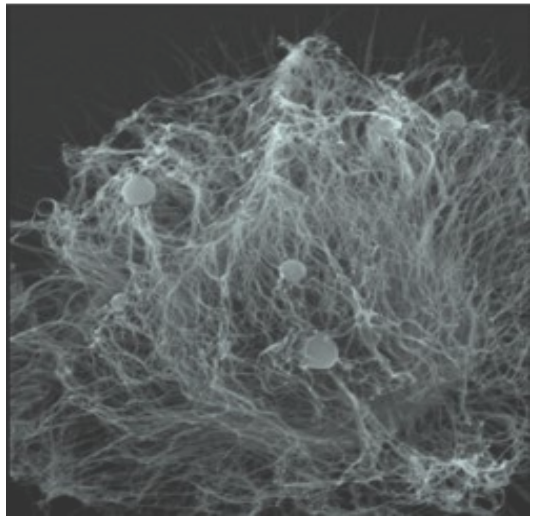
  - DoD CDMRP OR200187

NIH National Institute of Allergy and Infectious Diseases

CDMRP Department of Defense

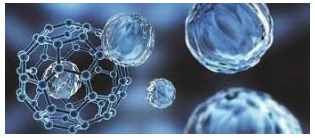




- ***Scientific advisor, shareholder***

MicroCures, Inc.

Zylö



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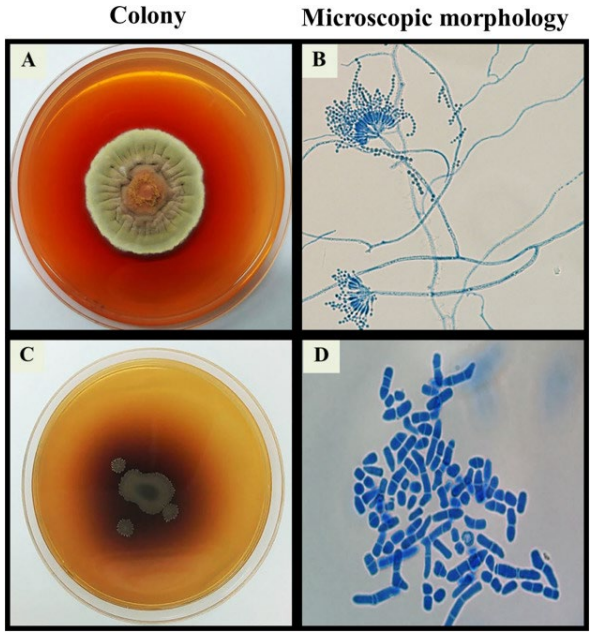
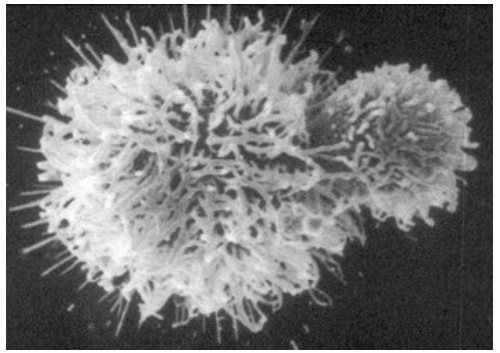
FUNGI: WHO CARES?

- **Fungi are ubiquitous**
- Since the late 1970s, fungi have emerged as major causes of human disease.
- It is estimated that more than **6 billion people** throughout the world have fungal infections with 15–30% of these infections being serious (https://gaffi.org/)
- Invasive mycoses contribute to ~**1.5 million human deaths** each year.
- Invasive mycoses are responsible for >$6.7 billion in human medical care costs annually in USA (2018 data)
- Total costs of all fungal-related hospital stays >$37 billion.
- Mortality rates of invasive mycoses often in excess of 40%



Talaromyces marneffei



Cryptococcus

Open Forum Infectious Diseases
MAJOR ARTICLE
IDSA Infectious Diseases Society of America
hivma hiv medicine association
Prevalence and Healthcare Burden of Fungal Infections in the United States, 2018
January 10, 2022
https://doi.org/10.1093/ofid/ofab593

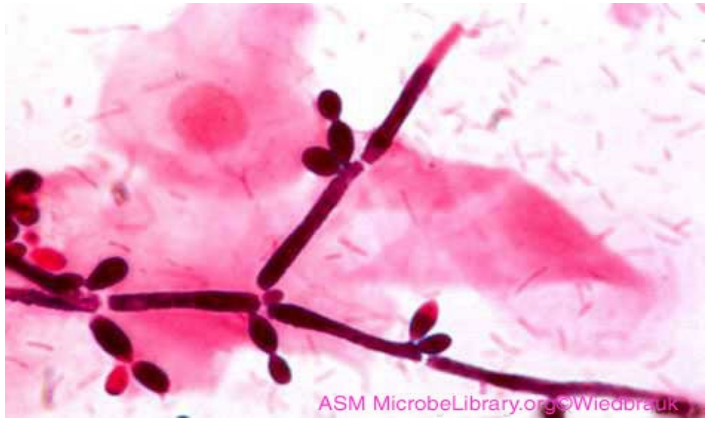
THE FUNGI

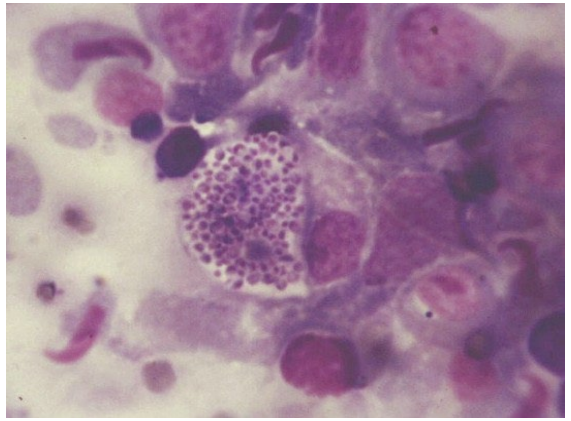
>1,500,000 species

~300 are mammalian "pathogens"

~20-30 are <u>common</u> invasive human pathogens

Armillaria ostoyae (honey mushroom)
~3.5 miles across





FUNGI: THE GOOD AND THE BAD

Poster from 1880s

THE FUNGI

ECOSYSTEM
DIGEST ORGANIC MATTER

PLANT DISEASES
DUTCH ELM DISEASE
POTATO FAMINE
CORAL REEF BLEACHING

FOODSTUFFS
BEER
WINE
FOOD

TOXINS
LIVER CANCER
SICK BUILDING SYNDROME

DRUGS
PENICILLIN
CEPHALOSPORINS
CYCLOSPORINS
LOVOSTATIN
LSD, ERGOT

PATHOGENS
ANIMAL
INSECT
HUMAN

Adapted from A. Casadevall

THE THERMAL BARRIER

PATHOGENICITY

< 0.00001%

mammals — 37 °C

ectotherm vertebrates

insects

plants

All fungi (>1,500,000 species)

Cytrid die off, www.nationalgeographic.com; Matthew Fisher

Zombie ants, www.smithsonianmag.com; David Hughes

Chestnut blight, www.asm.org; Matt T. Kasson

Adapted from A. Casadevall

Climate change

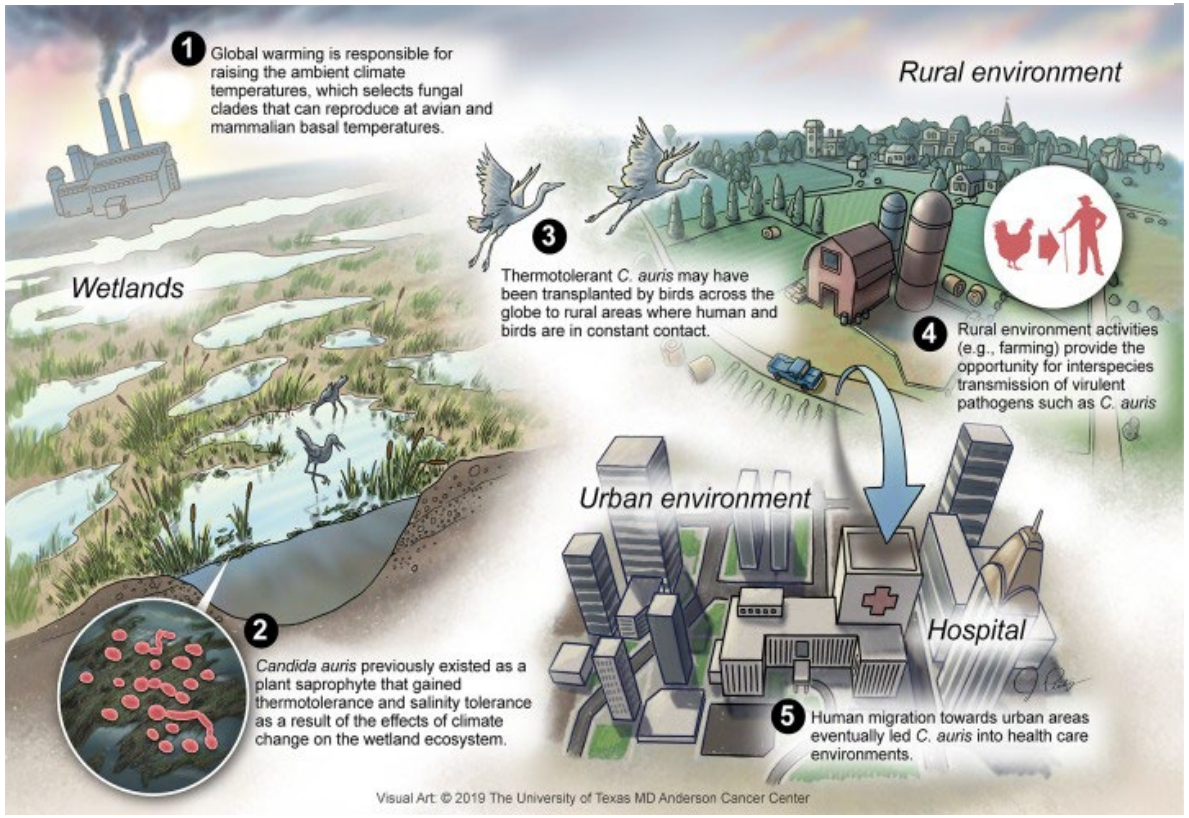
- An environmental “boot camp”
- Shifting geographic spread of pathogens, including fungi
- “New” fungi:
  - *Emergomyces*- a leading invasive dimorphic fungus in setting of advanced HIV disease in Africa
  - *Candida auris*- multi- to pan-resistant yeast first identified in 2009, now on all continents except Antarctica.

AMERICAN SOCIETY FOR MICROBIOLOGY | mBio®

OPINION/HYPOTHESIS
Host-Microbe Biology
July/August 2019 Volume 10 Issue 4 e01397-19
https://doi.org/10.1128/mBio.01397-19

On the Emergence of *Candida auris*: Climate Change, Azoles, Swamps, and Birds

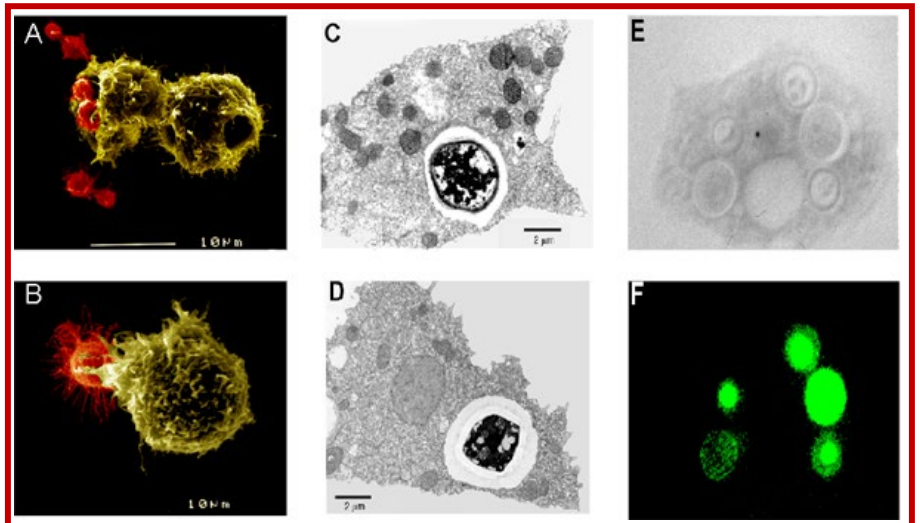
Arturo Casadevall [a], Dimitrios P. Kontoyiannis [b], Vincent Robert[c]



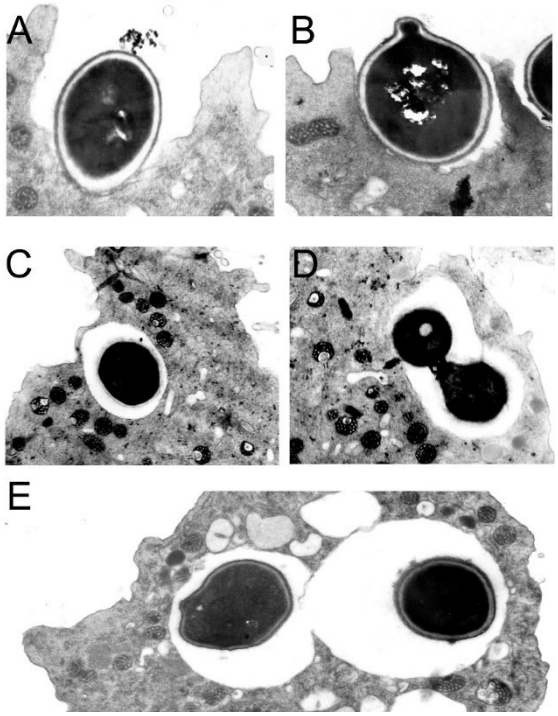
Why do environmental fungi cause disease in humans (dead-end hosts)?

-How are environmental pathogens able to effectively infect humans?

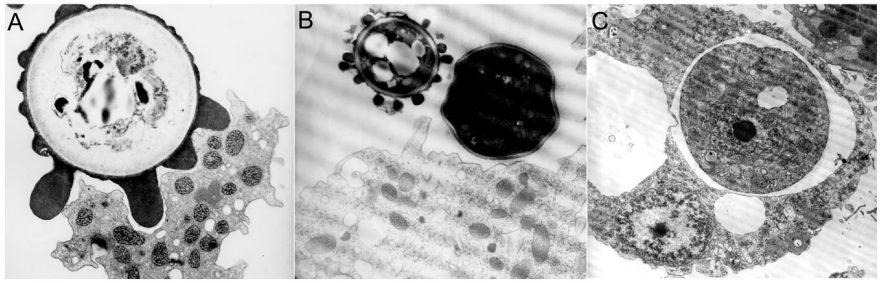
-How do environmental pathogens maintain their virulence?



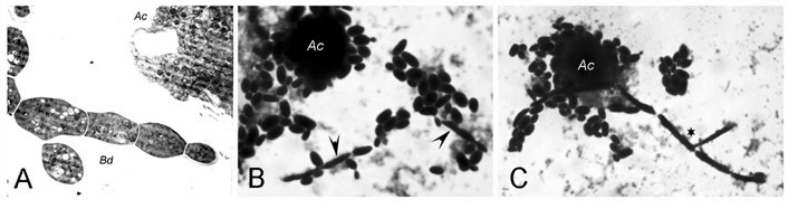
Steenbergen et al, PNAS 2001



H. capsulatum



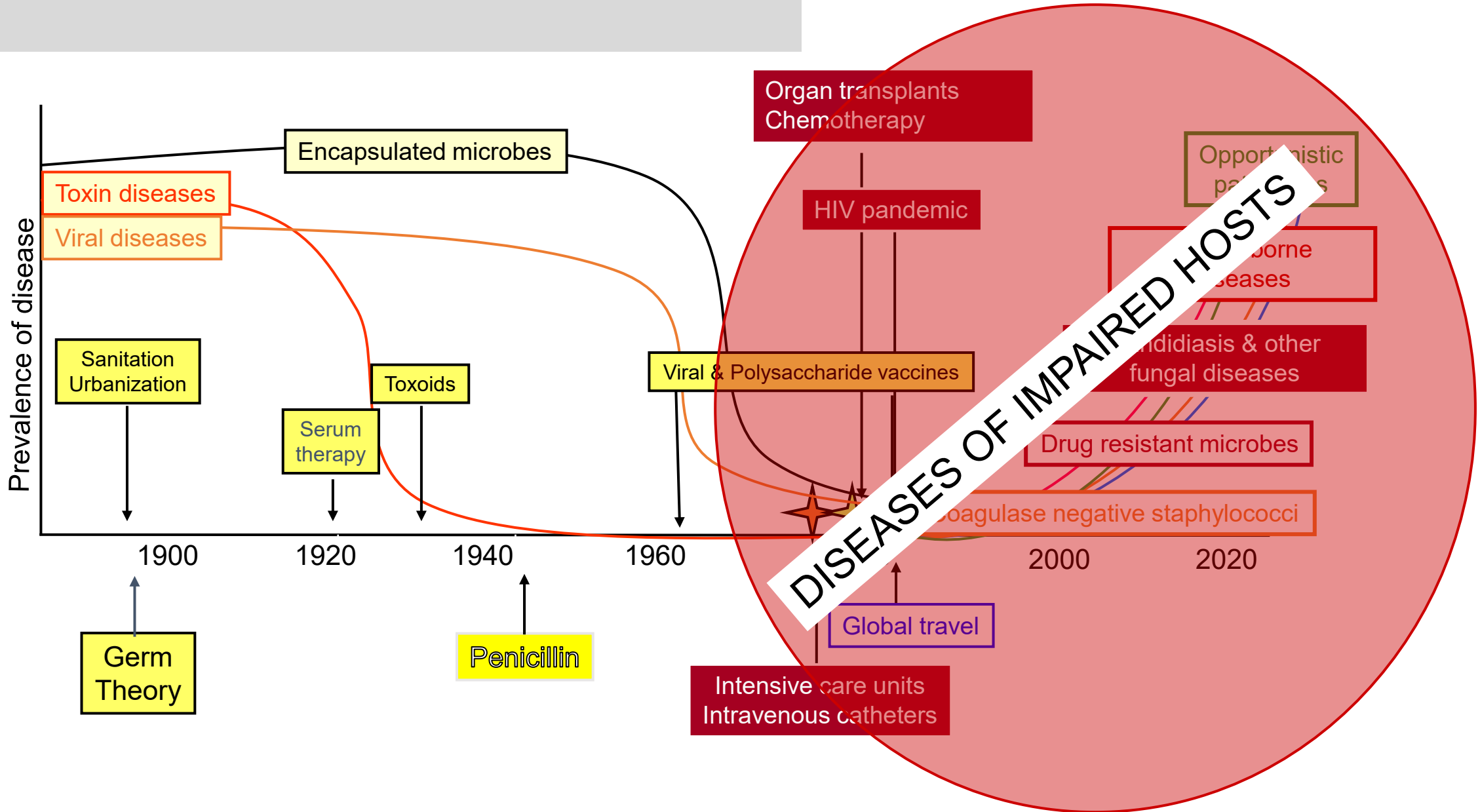
H. Capsulatum A & B] conidia, C] yeast



A] *B. dermatitidis*, B &C] *H. capsulatum*

Nosanchuk et al, Infect Immunity 2004

Infectious diseases 1900-2022



Many new risks: age of the biologics!

Table 1. Biological therapies associated with fungal infection susceptibility in humans.

Biological agent	Drug target	FDA-approved indication(s)	Fungal infection susceptibility	Mechanism(s) of fungal infection susceptibility (when known)
Alemtuzumab	CD52	CLL, MS	Mucosal candidiasis, PJP, cryptococcosis	Profound and prolonged T cell lymphopenia
Rituximab	CD20	CLL, NHL, RA, microscopic polyangiitis, Wegener's granulomatosis	PJP	B cell lymphopenia, impaired T cell responses
Tocilizumab	IL-6R	RA, JIA, giant cell arteritis, cytokine release syndrome (CAR T cell therapy)	Invasive candidiasis, PJP, cryptococcosis, coccidioidomycosis	Impaired phagocyte recruitment and function (*Candida*)
Secukinumab Ixekizumab	IL-17A	Psoriasis, psoriatic arthritis, AS	Mucosal candidiasis	Impaired IL-17 cellular responses
Bimekizumab	IL-17A/IL-17F	N/A		
Brodalumab	IL-17RA	Psoriasis		
Ustekinumab	IL-12p40	Psoriasis, psoriatic arthritis, CD, UC		
Guselkumab Risankizumab Tildrakizumab	IL-23p19	Psoriasis CD		
Infliximab Adalimumab Etanercept Certolizumabpegol Golimumab	TNF-α	Psoriasis, psoriatic arthritis, RA, JIA, AS, CD, UC	IPA, invasive candidiasis, PJP, histoplasmosis, blastomycosis, coccidioidomycosis	Impaired IFN-γ production and granuloma formation (endemic fungi); impaired phagocyte recruitment and activation (*Candida* and *Aspergillus*)
Emapalumab	IFN-γ	HLH	PJP, coccidioidomycosis	Impaired IFN-γ cellular responses
Eculizumab	C5a	PNH, HUS	IPA, invasive candidiasis	Impaired phagocyte function
Ibrutinib Acalabrutinib	BTK	CLL/SLL, MCL, MZL, WM, GvHD	IPA*, mucormycosis, fusariosis, cryptococcosis, PJP, histoplasmosis, blastomycosis	Impaired macrophage activation (*Aspergillus*); impaired macrophage uptake and IgM production (*Cryptococcus*)
Ruxolitinib Baricitinib, Tofacitinib Upadacitinib	JAK1/2/3	Myelofibrosis, polycythemia vera, GvHD, RA, psoriatic arthritis, UC	IPA, PJP, cryptococcosis, talaromycosis, histoplasmosis	Impaired IFN-γ/STAT1 signaling and lymphopenia (endemic fungi); impaired IFN-λ signaling (*Aspergillus*)
Fostamatinib	Syk	ITP	Mucosal candidiasis, skin fungal infection	Impaired IL-17 cellular responses
Sorafenib	B-RAF C-Raf	HCC, RCC	IPA, mucosal candidiasis, *Rhodotorula* skin infection	Impaired ERK signaling (*Aspergillus*); impaired T cell responses (*Candida*, *Rhodotorula*)
Dasatinib	BCR-ABL	CML	PJP	Impaired T cell activation
Idelalisib	PI3K (p100δ)	CLL/SLL, NHL	PJP	Impaired T cell activation
Abatacept	CTLA4	RA, JIA	IPA, invasive candidiasis, PJP, histoplasmosis	Impaired T cell activation (PJP, histoplasmosis)
Natalizumab	$\alpha_4$integrin	MS	Cryptococcosis	T cell trafficking

IPA, invasive pulmonary aspergillosis (*with significant proportion of patients developing disseminated disease, including in the central nervous system); PJP; *Pneumocystis jirovecii* pneumonia; CLL, chronic lymphocytic leukemia; SLL, small lymphocytic leukemia; CML, chronic myelogenous leukemia; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; NHL, Non-Hogdkin's lymphoma; WM, Waldenström macroglobulinemia; HLH, hemophagocytic lymphohistiocytosis; PNH, paroxysmal nocturnal hemoglobinuria; HUS, hemolytic uremic syndrome; RCC, renal cell carcinoma; HCC, hepatocellular carcinoma; ITP, idiopathic thrombocytopenic purpura; MS, multiple sclerosis; RA, rheumatoid arthritis, JIA, juvenile idiopathic arthritis; AS, ankylosing spondylitis; UC, ulcerative colitis; CD, Crohn's disease; GvHD, graft-versus-host disease; CAR, chimeric antigen receptor; BTK, Bruton's tyrosine kinase; JAK, Janus kinase; Syk, spleen tyrosine kinase; RAF, rapidly accelerated fibrosarcoma; PI3K, phosphoinositide 3-kinase; CTLA4, cytotoxic T-lymphocyte associated protein 4; N/A, not available.

Courtesy of M. Lianakis, NIH, in 2021

WHO fungal priority pathogens list
October 25, 2022

Critical group


Cryptococcus neoformans


Candida auris


Aspergillus fumigatus


Candida albicans

Focus on fungi that cause systemic infections with treatment challenges.
Health inequities.
Purpose: to drive and focus research & policies in the global response to fungal infections and resistance.

High group


Nakaseomyces glabrata (Candida glabrata)


Histoplasma spp.


Eumycetoma causative agents


Mucorales


Fusarium spp.


Candida tropicalis


Candida parapsilosis

Medium group


Scedosporium spp.


Lomentospora prolificans


Coccidioides spp.


Pichia kudriavzeveii (Candida krusei)


Cryptococcus gattii


Talaromyces marneffei


Pneumocystis jirovecii


Paracoccidioides spp.

Table 2. Prioritization criteria, definitions and levels

Criterion	Definition/description	Level value
 Deaths	Average case fatality rate	**Low:** < 30% **Medium:** 30–70% fatality **High:** > 70% **Unknown:** no reliable data
 Annual incidence	Number of new cases per million population each year	**Low:** < 2/million **Medium:** 2–50/million **High:** > 50/million **Unknown:** no data available
 Current global distribution	Extent of geographic distribution across the globe	**Localized** in ≤ 2 WHO regions **Globally distributed** in ≥ 3 WHO regions **Unknown:** due to inadequate data
 Trends in last 10 years	Evidence of change in incidence/prevalence patterns	**Stable:** no evidence of increasing incidence/prevalence **Increasing:** evidence of increasing incidence/prevalence **Unknown:** due to inadequate data
 Inpatient care	Average length of hospital stay required for treatment following initial diagnosis	**Low:** < 2 days **Medium:** 2 days to 2 weeks **High:** > 2 weeks **Unknown:** no data available
 Complications and sequelae	Proportion of patients suffering long-term complications of disease	**Low:** expected to affect a minority of patients (e.g. < 10%). **Medium:** expected to affect a significant proportion of patients (e.g. 10–50%). **High:** expected to affect the majority of patients (e.g. > 50%).
 Antifungal resistance	Rate (or level) of acquired or intrinsic resistance to antifungal treatment	**Low:** < 10% acquired or intrinsic resistance for all four classes of antifungals. **Medium:** acquired or intrinsic resistance (> 10%) described for agents from one to two classes of antifungals. **High:** acquired or intrinsic resistance (> 10%) described for agents from three to four classes of antifungals. **Unknown:** no reliable data available
 Preventability	Transmission/ acquisition dynamics and availability of evidence-based, effective preventive measures	**Low:** transmission/acquisition dynamics well described, and preventive measures ineffective or of low-quality evidence, and/or not widely available or difficult to implement. **Medium:** transmission/acquisition dynamics are not well described, but preventive measures based on moderate or high-quality evidence are available and effective. **High:** transmission/acquisition dynamics are well described, and preventive measures based on moderate or high-quality evidence are universally available and effective. **Unknown:** transmission/acquisition dynamics not well described. No preventive measures described.
 Access to diagnostic tests	Availability of diagnostics	**Low:** diagnostics are not available in reference laboratories. **Medium:** diagnostics are available in institutional or reference laboratories but not universally available due to cost, distribution or technical issues. **High:** diagnostics are available and have been successfully implemented in institutional diagnostic laboratories, in at least one but not all high-burden/low-resource settings where disease occurs. **Very high:** diagnostics are universally available in institutional diagnostic laboratories where disease occurs.
 Evidence-based treatments	Treatment options are evidence based and accessible	**Very low:** treatment based on expert opinion with limited evidence. **Low:** peer-reviewed, high-quality guidelines available, but first-line treatment options are unaffordable, toxic or unavailable where disease occurs. **Medium:** peer-reviewed, high-quality guidelines with at least one first-line treatment option which is affordable, non-toxic and available where disease occurs. **High:** peer-reviewed, high-quality guidelines with at least one first-line treatment option which is affordable, nontoxic and available where disease occurs, and includes specific recommendations for all main host groups, including paediatrics.

WHO fungal priority pathogens list
October 25, 2022

Critical group


Cryptococcus neoformans


Candida auris


Aspergillus fumigatus


Candida albicans

High group


Nakaseomyces glabrata (Candida glabrata)


Histoplasma spp.


Eumycetoma causative agents


Mucorales


Fusarium spp.


Candida tropicalis


Candida parapsilosis

Medium group


Scedosporium spp.


Lomentospora prolificans


Coccidioides spp.


Pichia kudriavzeveii (Candida krusei)


Cryptococcus gattii

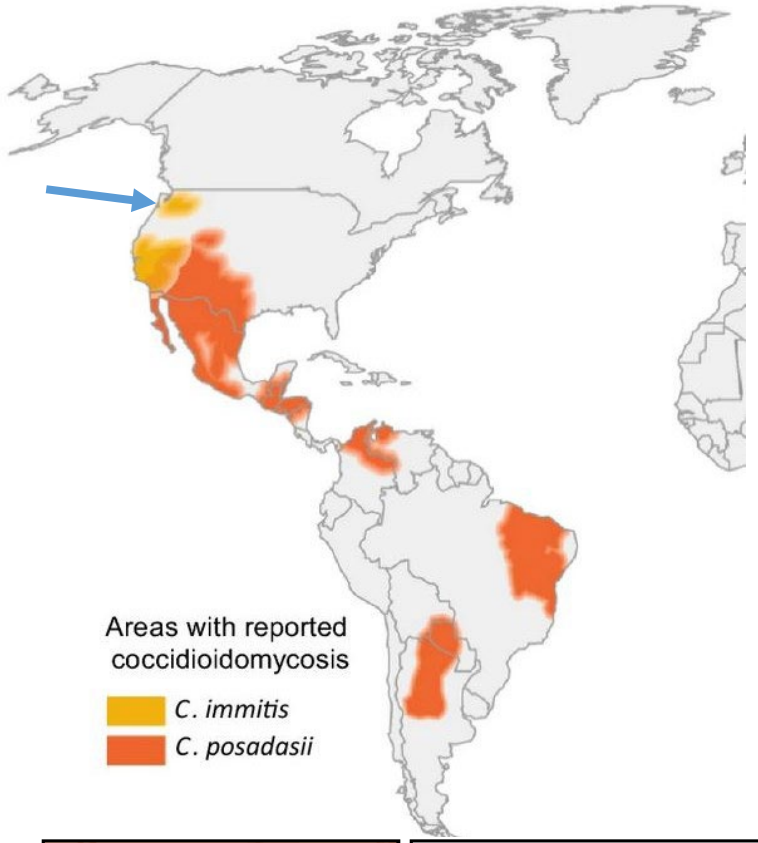

Talaromyces marneffei


Pneumocystis jirovecii

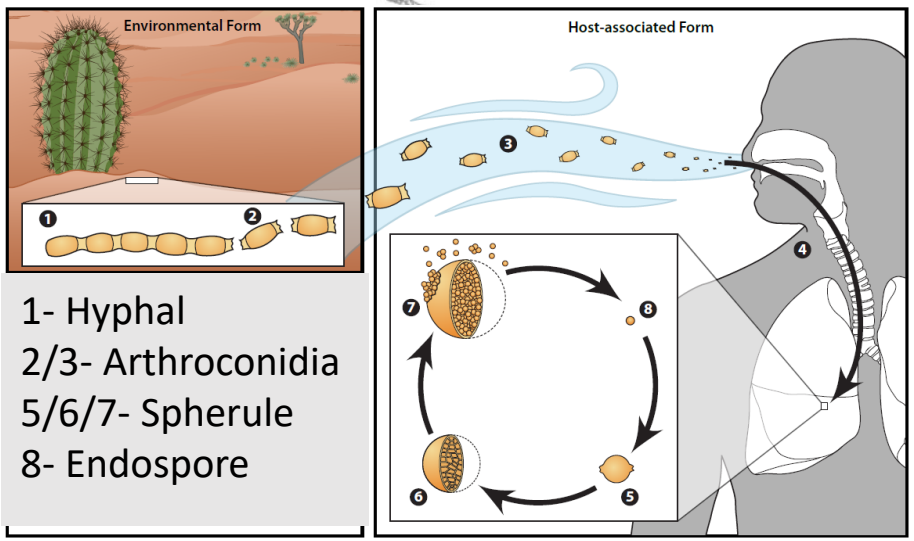

Paracoccidioides spp.

“Valley Fever”

- Coccidioidomycosis is caused by two highly similar species
  - *Coccidioides immitis*
  - *C. posadasii*
- *C. immitis*- responsible for “Valley Fever”
  - *95% US Cases are in southern Arizona and the San Joaquin Valley region in California.*
- *Coccidioides spp.* are **dimorphic** organisms that infect mammals through the respiratory track after disturbances in the environment:
  - earthquakes, construction, military activities, dirt bikes, armadillo-hunting, etc

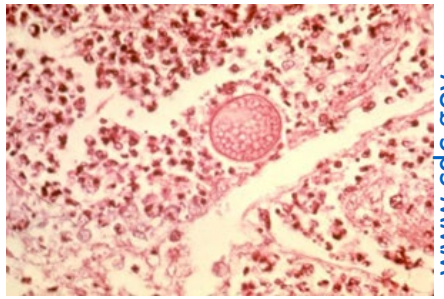


N. Ashraf et al, Mycopathologia (2020) 185:843–865
Re-drawing the Maps for Endemic Mycoses

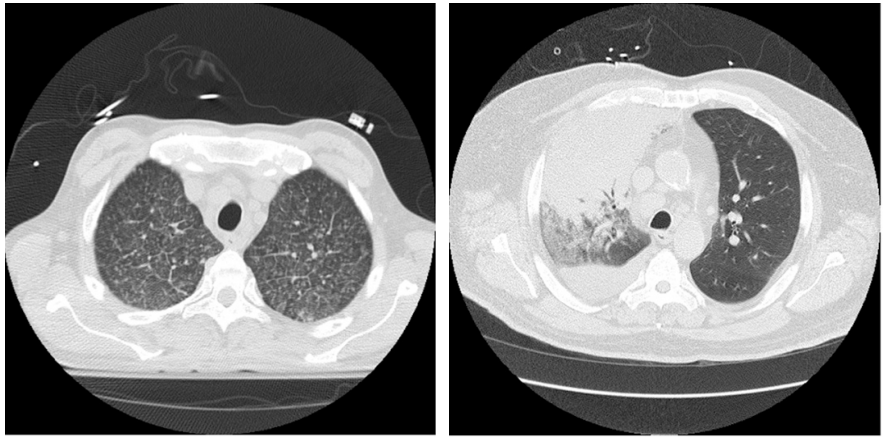


https://www.cdc.gov/fungal/diseases/coccidioidomycosis/causes.html

“Valley Fever”

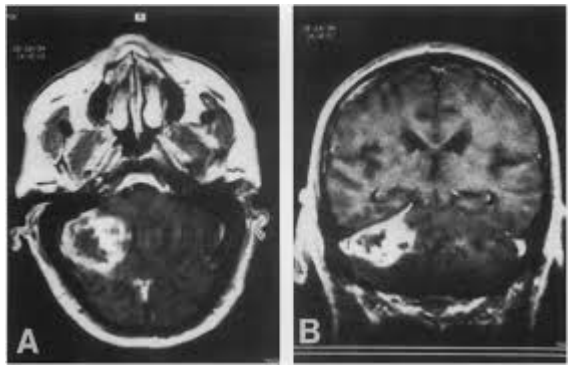


www.cdc.gov

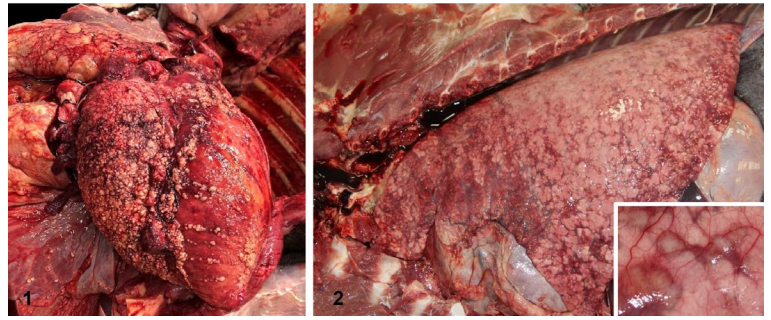


Malo et al, Ann Am Thorac Soc, 2014

- ~40% of exposed humans develop fever, cough, etc.
- ~5-10% will have more significant disease, especially pneumonia.
- ~1% will develop serious disease, including meningitis.
- There are **~200 deaths annually.**
- Average cost of hospitalization: ~$50,000 (CDC data)
- In 2019, there were **>20,000 patients** with coccidioidomycosis in the US
  - Incidence is increasing over past decades.
- Coccidioidomycosis is also a significant cause of morbidity and mortality in animals.
  - Pneumonia, osteomyelitis, skin, etc



Bañuelos, et al CID, 1996

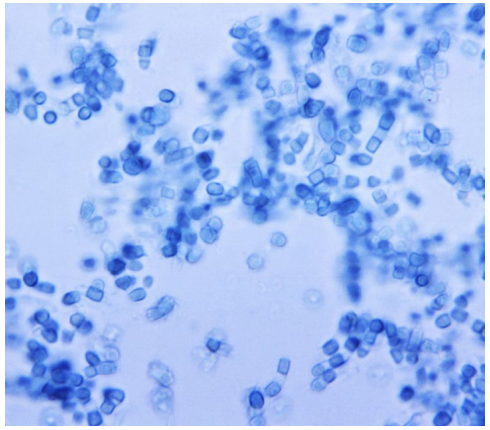


Coccidioidomycosis in 26 horses in California, USA: case series and review of the literature

Journal of Veterinary Diagnostic Investigation
2022, Vol. 34(6) 995–999

DOI: 10.1177/10406387221114622

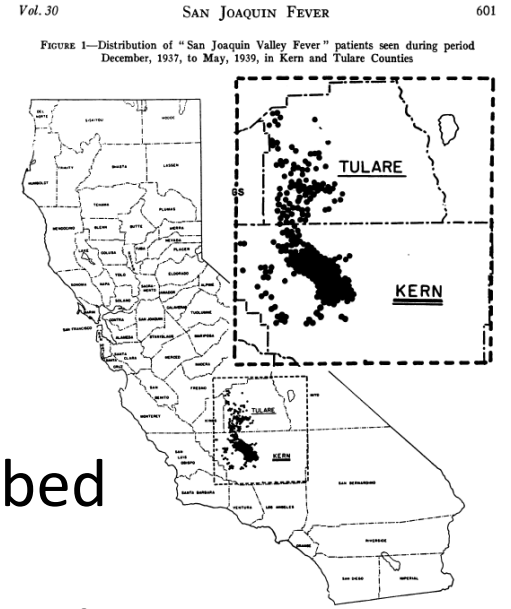
Coccidioides challenges: examples



www.cdc.gov

- Climate change- geographic expansion.
- *Coccidioides spp.* infect “healthy” individuals- anyone can get it!
- Immunologically compromised are more likely to develop severe disease.
  - Immune system sees different forms- arthroconidia, endospores, & spherules
- Structural determinants- certain groups of individuals more likely to be exposed.
- Limited antifungal arsenal and lack of approved vaccine.
- Antifungal resistance- particular concerns with high MIC for fluconazole.
- High virulence and easy spread with disturbance of colonies in the microbiology laboratory complicate antifungal testing.
- Lack of disease reporting in many states (only reportable in **26**, plus DC) and low rates of reporting in Latin America.
- Lack of sensitive/specific rapid testing and low rates of screening.

So, the time to address coccidioidomycoiss **is now!**
(*& a quick history lesson*)



Vol. 30 SAN JOAQUIN FEVER 601

FIGURE 1—Distribution of "San Joaquin Valley Fever" patients seen during period December, 1937, to May, 1939, in Kern and Tulare Counties

Epidemiology of Acute Coccidioidomycosis with Erythema Nodosum*
("San Joaquin" or "Valley Fever")
CHARLES EDWARD SMITH, M.D., D.P.H.

AMERICAN JOURNAL OF PUBLIC HEALTH *June, 1940*

- **1982**: Alejandro Posadas, an intern in Buenos Aires, Argentina described a 36-year-old soldier with cutaneous disease. Histology revealed a protozoan-like organism, *Coccidia*. Disease was successfully transmitted by injecting material from the patient into mammals.
- 1983: first report of a patient in San Francisco.
- 1896: named *Coccidioides (*resembling *Coccidia) immitis (*not mild*).*
- 1900: Dimorphism confirmed that this was a **fungus**.
- **1929**: Second year medical student, Harold Chope, opened a plate with *C. immitis* in a Stanford University laboratory and developed "**Valley Fever**"

September, 1937 VALLEY FEVER

ORIGINAL ARTICLES

"VALLEY FEVER" OF THE SAN JOAQUIN VALLEY AND FUNGUS COCCIDIOIDES*

By ERNEST C. DICKSON, M.D.
San Francisco

DISCUSSION *by K. F. Meyer, M.D., Ph.D., San Francisco; Hiram E. Miller, M.D., San Francisco; Roland B. Tupper, M.D., Fresno.*

CALIFORNIA AND WESTERN MEDICINE Vol. 47, No. 3