Endemic Mycoses in The Asia-Pacific Region

Methee Chayakulkeeree, MD, PhD, FECMM
Associate Professor
Division of Infectious Diseases and Tropical Medicine
Department of Medicine, Faculty of Medicine Siriraj Hospital
Mahidol University
BANGKOK, THAILAND

Disclosure

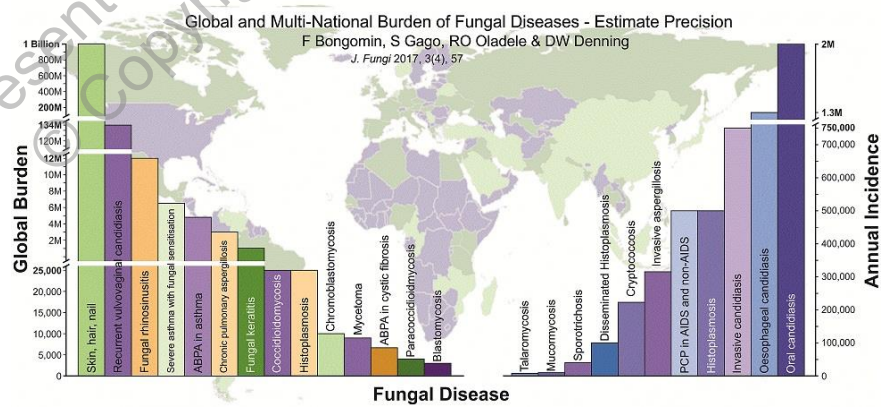
- **Research grants**: Pfizer, Siam Pharmaceuticals, MSD, Janssen, AstraZeneca
- **Speaker bureau**: Pfizer, LF Asia, Astellas, MSD, Siam Pharmaceuticals, Berlin, Roche
- **Travel grants**: Siam Pharmaceuticals, MSD, LF Asia, Astellas, Pfizer, Atlanta

Global Burden of Fungal Diseases

- Over 300 million people suffer from serious fungal-related diseases worldwide
- Fungi kill over 1.6 million people annually
  (> malaria and ~TB)
- About 1.5 million fungal species, 8000 cause diseases in plants and 300 are human pathogens

The Burden of Fungal Disease (LIFE, 2017); Mycol. Res. 2001;105:1422–32.

Global Fungal Burden



Ten Most Significant Fungal Infections

Disease (most common species)	Location	Estimated life-threatening infections/ year at that location*	Mortality rates (% in infected populations)*
Opportunistic invasive mycoses			
Aspergillosis (*Aspergillus fumigatus*)	Worldwide	>200,000	30–95
Candidiasis (*Candida albicans*)	Worldwide	>400,000	46–75
Cryptococcosis (*Cryptococcus neoformans*)	Worldwide	>1,000,000	20–70
Mucormycosis (*Rhizopus oryzae*)	Worldwide	>10,000	30–90
Pneumocystis (*Pneumocystis jirovecii*)	Worldwide	>400,000	20–80
Endemic dimorphic mycoses*†			
Blastomycosis (*Blastomyces dermatitidis*)	Midwestern and Atlantic United States	~3,000	<2–68
Coccidioidomycosis (*Coccidioides immitis*)	Southwestern United States	~25,000	<1–70
Histoplasmosis (*Histoplasma capsulatum*)	Midwestern United States	~25,000	28–50
Paracoccidioidomycosis (*Paracoccidioides brasiliensis*)	Brazil	~4,000	5–27
Penicilliosis (*Penicillium marneffei*)	Southeast Asia	>8,000	2–75

*Most of these figures are estimates based on available data, and the logic behind these estimates can be found in the text and in the Supplementary Materials. †Endemic dimorphic mycoses can occur at many locations throughout the world. However, data for most of those locations are severely limited. For these mycoses, we have estimated the infections per year and the mortality at a specific location, where the most data are available.

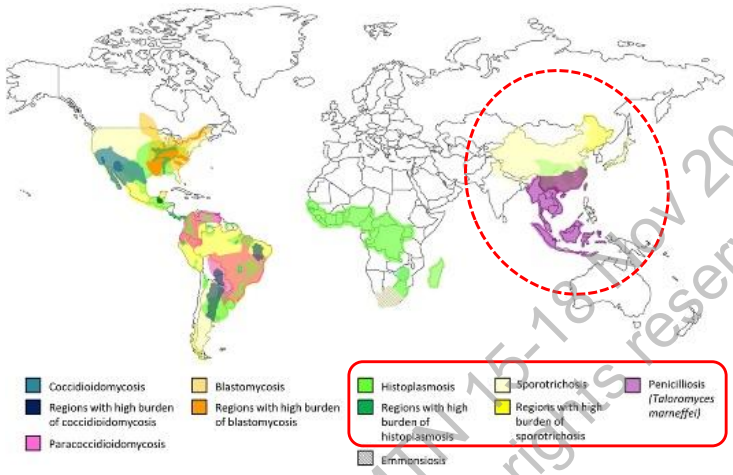
Sci Transl Med 2012;4

Endemic Mycoses

- A group of diseases caused by diverse fungi that share common characteristics
  - Occupy a specific etiologic niche in the environment
  - Dimorphic in nature (yeast or spherule form in tissue and mycelial form in the environment)
    - ? What about *Cryptococcus gattii*
  - Able to produce infection in healthy hosts

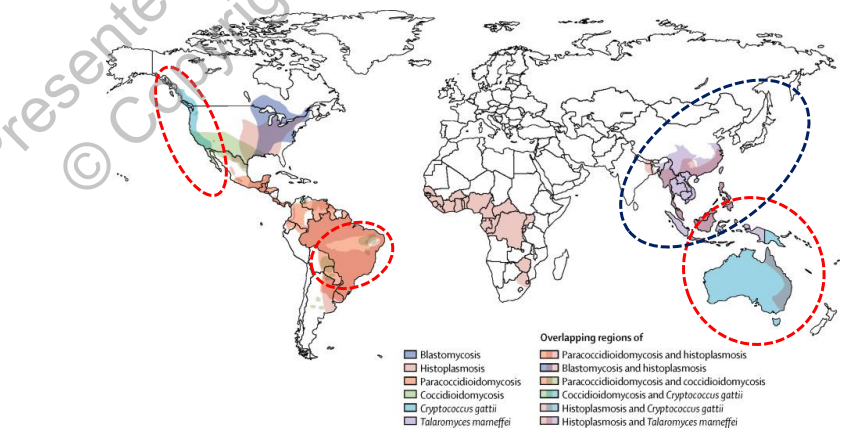
Med Mycol May 2011, 49, 337–344

Distribution of Endemic Mycoses



Front. Immunol. 8:735. doi: 10.3389/fimmu.2017.00735

Distribution of Endemic Mycoses and *Cryptococcus gattii* Infection

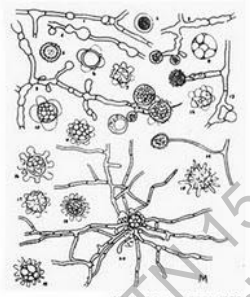


Lancet Neurol 2018; 17: 362–72

Histoplasmosis

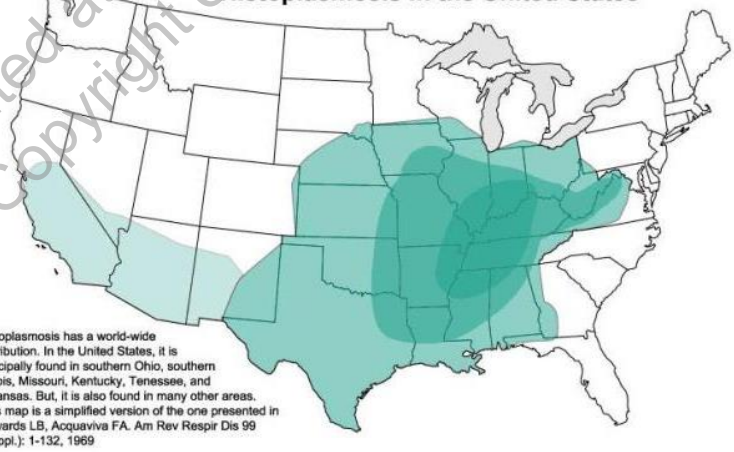
- Discovery of *H. capsulatum* in 1905 by Samuel Darling, a pathologist in Panama
- Isolated from a young man diagnosed as miliary tuberculosis

Samuel Darling (1872-1925)



Histoplasma, Moore 1935

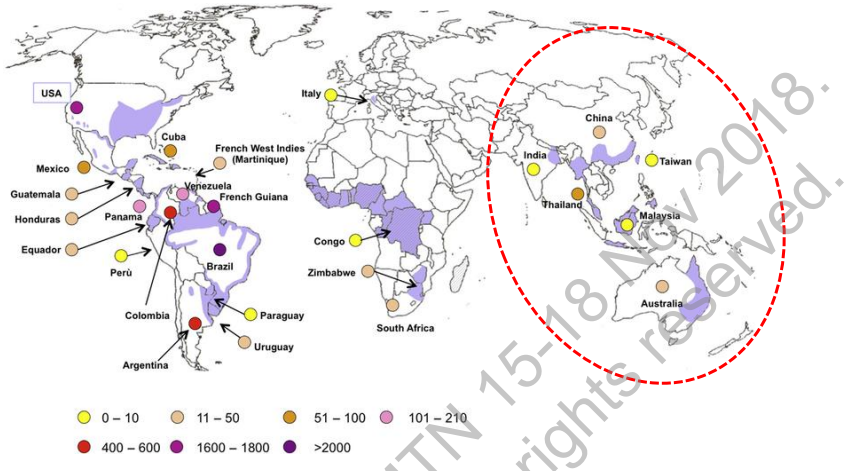
Simplified Map of the Distribution of Histoplasmosis in the United States



Histoplasmosis has a world-wide distribution. In the United States, it is principally found in southern Ohio, southern Illinois, Missouri, Kentucky, Tenessee, and Arkansas. But, it is also found in many other areas. This map is a simplified version of the one presented in Edwards LB, Acquaviva FA. Am Rev Respir Dis 99 (Suppl.): 1-132, 1969

www.doctorfungus.org

World Distribution of Histoplasmosis
- Microfoci-



Infect Dis Clin N Am 30 (2016) 207–227

Prevalence: Histopasmin Skin Test

Overall positivity 5 – 14 %

- Malaysia; 3% (children)
- Northern India; 0 – 12.3%
- Philippines; 26%
- China; range from 6%-50% (75% of disease cases - along Yangtze River)
  - Higher in Hunan and Jiangsu provinces (southeast China) than Xinjiang Autonomous region (northeast China)
  - Sichuan Province
    - 35% in southern part vs. 6% in northern
  - 17% has also been reported in east-central China

Indian J Chest Dis Allied Sci 1994; 36 : 193 – 213. Chin Med J (Engl) 2001; 114 :743 – 746. Am J Trop Med Hyg 1971; 20 : 288 – 319. Med J Malaya1968; 23 : 295 – 298. Mycopathologia 2001; 149 : 69 – 71. J Med Vet Mycol 1996; 34 : 171 – 174. Bing Xue Za Zhi 1998; 19 : 215 – 217

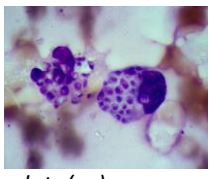
Source of Exposure to *H. capsulatum*

- Farming
- Exposure to chicken coops or caves
- Remodeling or demolition of old buildings
- Cutting down trees or clearing brush from sites in which blackbirds have roosted

Infect Dis Clin N Am 30 (2016) 207–227

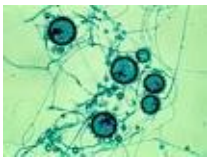
Histoplasma capsulatum

- Found in soil, bird and bat droppings
- Thermally dimorphic
- Heterothallic form [(+) and (-)]
  - *Histoplasma capsulatum* vs. *Ajellomyces capsulata(us)*



37°C

- 5 clades
  - Class 1 and Class 2 North Americans (class 1-less virulent)
  - South American Group A and Group B (often produce skin lesions)
    - *H. capsultum* var. *farciminosum* (Group A)
  - Central American
  - *H. capsulatum* var. *duboisii* (African histoplasmosis)



25°C

Med Mycol May 2011, 49, 337–344

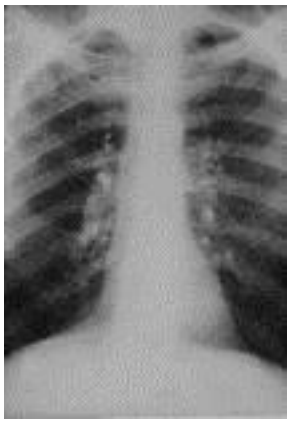
Acute pulmonary histoplasmosis

- Incubation period 14 days (7-21 days)
- Asymptomatic or flu-like illness
  - Fever, headache, non-productive cough, chest pain
  - Extrapulmonary S&S: arthralgia, erythema nodosum, erythema multiforme
- Resolve within 10 days (>90% unrecognized)
- Chest radiograph
  - Mediastinal or nodes enlargement
  - Patchy infiltrates
  - Calcifications

Infect Dis Clin N Am 30 (2016) 207–227

Complication of Pulmonary Histoplasmosis

- Pericarditis
- Pulmonary calcifications
- Mediastinal lymphadenitis
- Mediastinal granuloma
- Mediastinal fibrosis

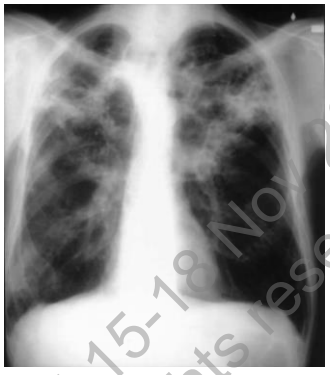


Brocholithiasis
(+/- liver and splenic calcifications)

Infect Dis Clin N Am 30 (2016) 207–227

Chronic Pulmonary Histoplasmosis

- **Cavitary**
  - Low-grade fever, weight loss
  - Productive cough
  - Dyspnea, chest pain (early)
  - Hemoptysis (late)
  - **CXR**: patchy infiltrates,consolidation and cavitation
- **Noncavitary**
  - Cough
  - Weight loss
  - Fever and chill
  - **CXR**: nodules, infiltrates, lymphadenopathy



Infect Dis Clin N Am 30 (2016) 207–227

Progressive Disseminated Histoplasmosis

- Immunocompromised hosts: HIV, hematologic malignancies, immunosuppressive therapy
- Multiple organ involvement
  - Lungs: cough, patchy pneumonitis, hilar/mediastinal lymphadenopathy
  - GI: uropharyngeal ulcer, diarrhea, hepatosplenomegaly
  - Blood: cytopenia
  - CNS: meningitis, cerebritis, mass lesions
  - Endovascular: endocarditis
  - Adrenal glands

Infect Dis Clin N Am 30 (2016) 207–227

Progressive Disseminated Histoplasmosis

	Acute	Subacute	Chronic
Fever/ weight loss	> 90% (abrupt onset)	50% (prolonged)	<30% (mild)
Hematologic disturbances	80%	40% (20% low plt)	Not significant
Hepato-splenomegaly	common	common	30%
Oropharygeal ulcers	< 20%	Deeper, malignancy-like	50% (well circumscribed, indurated, deep, painless)
Pulmonary involvement	Patchy infiltrates, mediastinal and hilar node enlargement	Less common	Less common

Infect Dis Clin N Am 30 (2016) 207–227

Progressive Disseminated Histoplasmosis

	Acute	Subacute	Chronic
Skin	-10% (MP rash, petechiae, papules, ecchymosis) - 60% in South American strains (papule with crust, nodule, pustule)		
GI tract	Colonic mass, perianal ulcers	40% ulceration at small and large bowel (terminal ileum and cecum)	
CNS	20% (meningitis, encephalitis)	Chronic meningitis, mass lesions, cerebritis	Chronic meningitis

Infect Dis Clin N Am 30 (2016) 207–227

Progressive Disseminated Histoplasmosis

	Acute	Subacute	Chronic
Endovascular		Endocarditis (left-sided > right-sided, aortic valve- most common)	
Adrenal glands		- 30-50% adrenal involvement (80% by autopsy - Usually asymptomatic -Addison's disease < 10%	
Others	- Sepsis-like - Reactive hemophagocytic syndrome		Bone infection

Infect Dis Clin N Am 30 (2016) 207–227

Progressive Disseminated Histoplasmosis

A 40-Year-Old Man

- Anti-HIV positive
- $CD4^+$ 46 cells/mm^3
- Low grade fever for 3 months
- Generalized lymphadenopathy

1 Month After Itraconazole Treatment

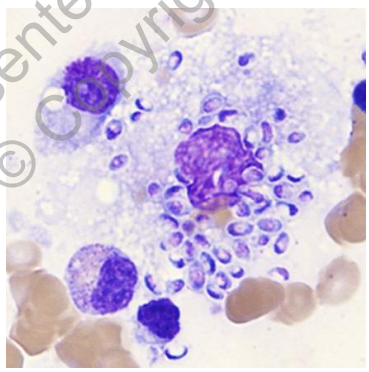
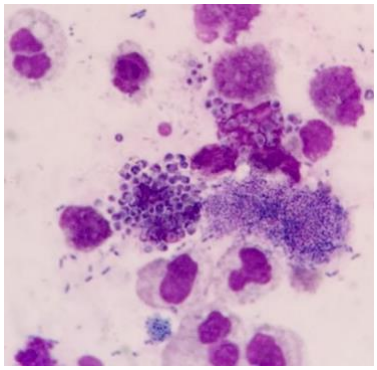
Cutaneous Lesions in Histoplasmosis



Molluskum-like

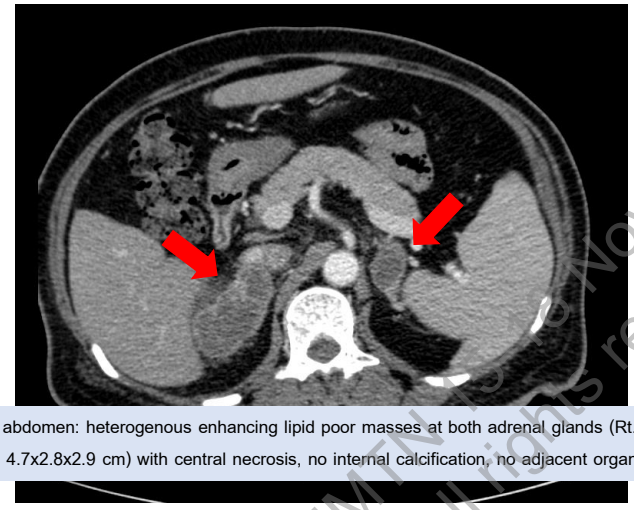
Phanuphak N ADR 2006;19:69-72

Diagnosis

Histoplasma capsulatum

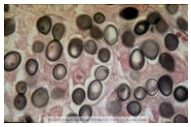
Adrenal Histoplasmosis in a 65-Year-Old Man

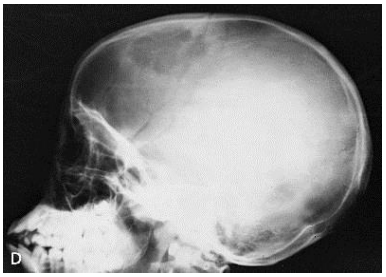


CT whole abdomen: heterogenous enhancing lipid poor masses at both adrenal glands (Rt. 4.2x3.1x3.2 cm, Lt. 4.7x2.8x2.9 cm) with central necrosis, no internal calcification, no adjacent organ invasion

African Histoplasmosis

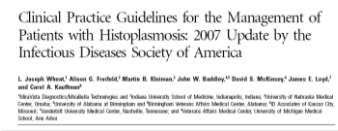
- Caused by *H. capsulatum var. duboisii* (larger yeast-15 µ, with thicker wall)
- Disseminated disease
- Skin and bone are the most frequent organ involved





Treatment of Disseminated Histoplasmosis

IDSA Guidelines 2007


Clinical Practice Guidelines for the Management of Patients with Histoplasmosis: 2007 Update by the Infectious Diseases Society of America

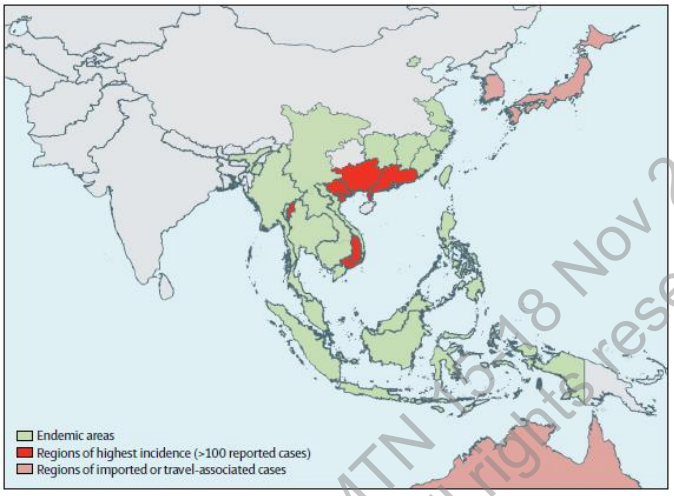
- Moderately severe to severe disease
  - Liposomal **amphotericin B** 3 mg/kg/day for 1-2 weeks, then itraconazole for at least 1 year (A-I)
  - Other lipid formulation of AmB 5 mg/kg/day for alternative of LAmB (A-III)
  - dAmB 0.7-1 mg/kg/day for alternative of LAmB (A-III)
- Mild-to-moderate disease
  - **Itraconazole** for at least 1 year (A-II)
- Lifelong suppressive therapy may be required in immunosuppressed patients (A-II)
  - Itraconazole 200 mg/day

Talaromycosis (Formerly Penicilliosis)

A 30 years old female
HIV+

Binary fission
Talaromyces marneffei

Geographic Distribution of Talaromycosis



Clinical Manifestation

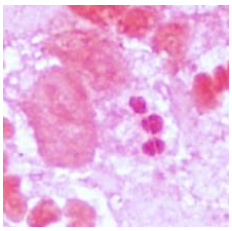
- Prolonged fever
- Weight loss
- Lymphadenopathy
- Hepatosplenomegaly
- Fungemia is common in patients with AIDS
- Skin lesions

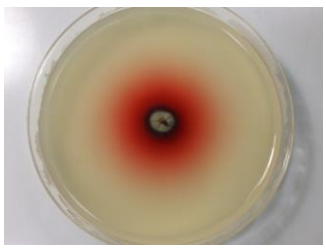
Cutaneous Lesions

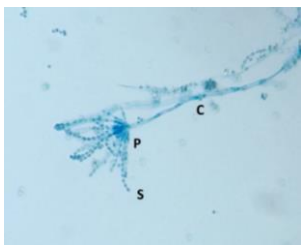
- Multiple discrete lesions
- Dome-shaped, skin-colored papules on erythematous base
- Central umbilication

Talaromycosis 50-85%
Histoplasmosis 30%
Cryptococcosis 10%

A Woman with Anti-Interferon Gamma Autoantibodies
(Newly recognized Risk Factor for Talaromycosis)



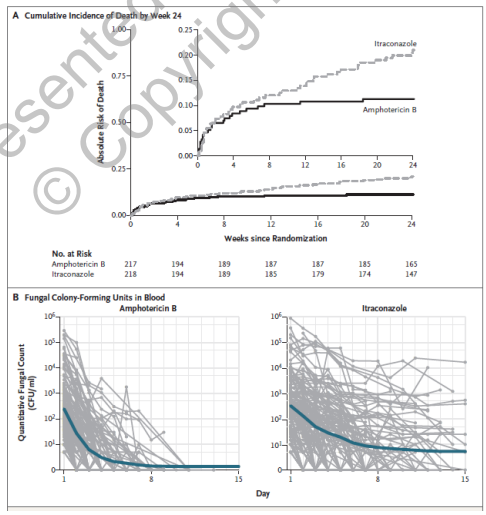




Fission Yeasts in Bone Marrow

Talaromyces marneffei

Treatment of Talaromycosis

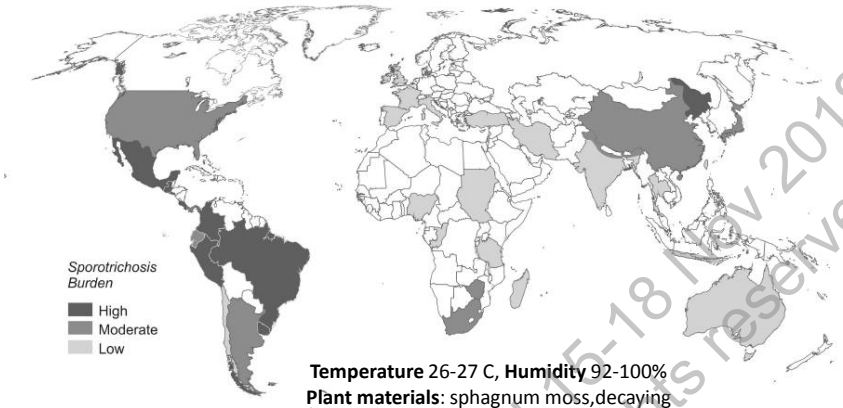


Amphotericin B

- Lower mortality at 24 weeks (but not 2 weeks)
- Faster clinical resolution and fungal clearance
- Lower rates of relapse and IRIS
- Higher side effects: infusion-related reactions, renal failure, hypokalemia, hypomagnesemia, and anemia

N Engl J Med 2017;376:2329-40.

Distributuon of Sporothricosis



Temperature 26-27 C, **Humidity** 92-100%
Plant materials: sphagnum moss,decaying vegetation, soil, hay, corn stalks

Medical Mycology, 2015, 53, 3–14

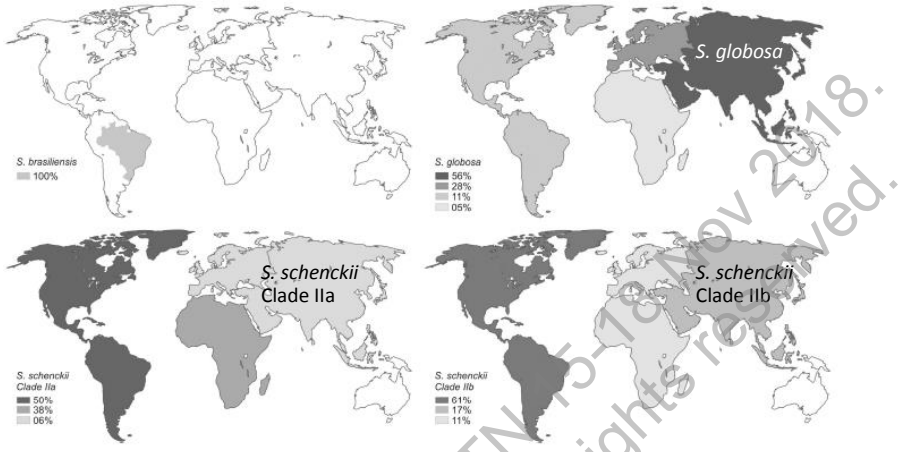
Sporothrix Schenckii

Now 6 species
3 clinically relevant
- *S. brasiliensis*
- *S. globosa*
- *S. luriei*
- *S. schenckii* sensu stricto

2 environmental fungi
- S. mexicana
- S. albicans

Fungal Diversity 2013:1–13.

Species Distribution of *Sporothrix* spp.



J Clin Microbiol 2006; 44: 3251–3256. Med Mycol 2008; 46: 621–625.

Four Forms of Sporothricosis

"Rose gardener's disease"

- Lymphocutaneous
  - usually unilateral
- Fixed cutaneous
- Multifocal or disseminated cutaneous
  - in immunosuppressed patients
- Extracutaneous
  - Example: lungs

Medical Mycology, 2015, 53, 3–14
Med Mycol May 2011, 49, 337–344

Cutaneous Sporothrichosis

Medical Mycology, 2015, 53, 3–14

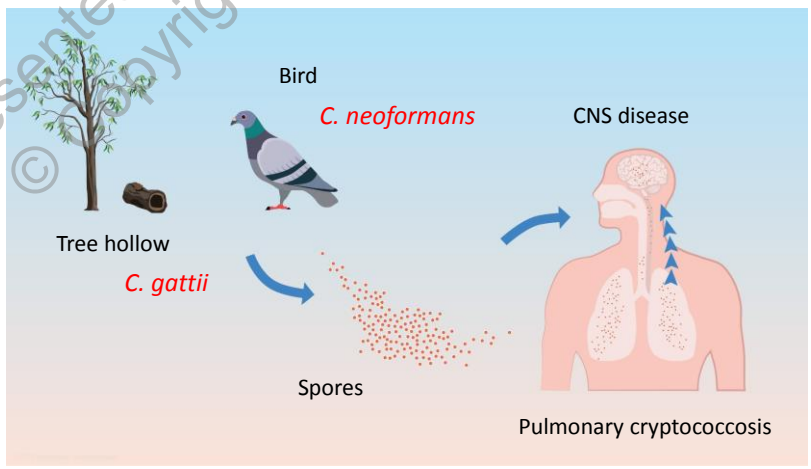
Treatment of Sporothrichosis

- **Cutaneous and lymphocutaneous sporotrichosis**:
  - Oral itraconazole 200 mg/d until 2-4 weeks after lesions resolved (3-6 months)
- **Osteoarticular sporotrichosis**:
  - Oral itraconazole 200 mg twice daily for 12 months
- **Pulmonary sporotrichosis**:
  - Severe, initial therapy should be liposomal amphotericin B 3-5 mg/kg/day; then oral itraconazole 200 mg twice daily for a minimum of 12 months
  - Initial therapy with itraconazole in less severe cases
- **Meningeal and disseminated sporotrichosis**:
  - Liposomal amphotericin B 5 mg/kg/day. then oral itraconazole 200 mg twice daily for a minimum of 12 months

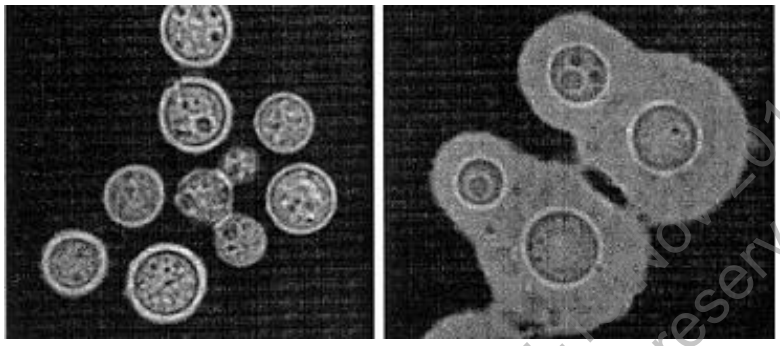
Clin Infect Dis. 2007; 45(10):1255-65

Cryptococcus gattii Infection

Pathgenesis of Cryptococcosis

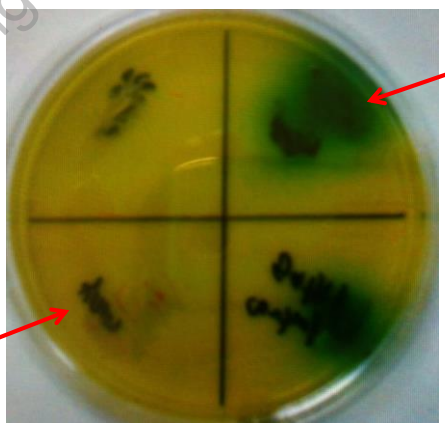


Cryptococcus gattii
The Giant Capsule



C. neoformans vs. *C. gattii*

L-canavanine glycine bromothymol blue (CGB) agar: *C. gattii*



Fungal Genetics and Biology 78 (2015) 16–48

Contents lists available at ScienceDirect

Fungal Genetics and Biology

journal homepage: www.elsevier.com/locate/yfgbi

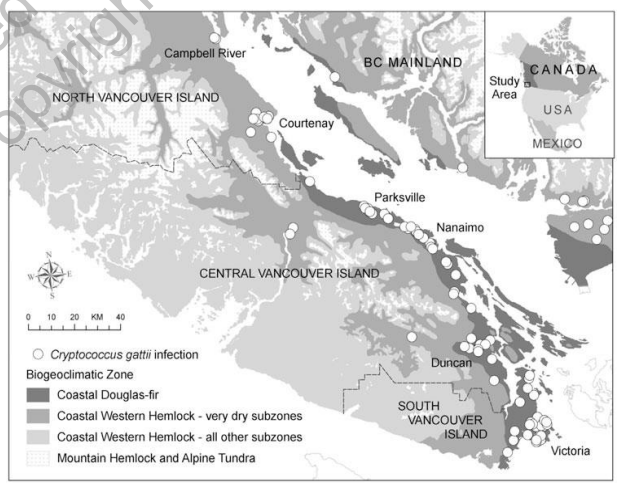
Recognition of seven species in the *Cryptococcus gattii*/*Cryptococcus neoformans* species complex

Ferry Hagen [a,b], Kantarawee Khayhan [a,c], Bart Theelen [a], Anna Kolecka [a], Itzhack Polacheck [d], Edward Sionov [d,e], Rama Falk [d,f], Sittiporn Parnmen [g], H. Thorsten Lumbsch [h], Teun Boekhout [a,i,j,*]

[a] CBS-KNAW Fungal Biodiversity Centre, Basidiomycete and Yeast Research, Utrecht, The Netherlands
[b] Department of Medical Microbiology and Infectious Diseases, Canisius-Wilhelmina Hospital, Nijmegen, The Netherlands
[c] Department of Microbiology and Parasitology, Faculty of Medical Sciences, University of Phayao, Phayao, Thailand
[d] Department of Clinical Microbiology and Infectious Diseases, Hadassah-Hebrew University Medical Center, Ein Kerem, Jerusalem, Israel
[e] Department of Food Quality & Safety, Institute for Postharvest and Food Sciences, Agricultural Research Organization, The Volcani Center, Bet Dagan, Israel
[f] Department of Fisheries and Aquaculture, Ministry of Agriculture and Rural Development, Nir-David, Israel
[g] Department of Medical Sciences, Ministry of Public Health, Nonthaburi, Thailand

Current species	Proposed species
Cryptococcus neoformans (serotypes A and D)	*Cryptococcus neoformans* *Cryptococcus deneoformans*
Cryptococcus gattii (serotypes B and C)	*Cryptococcus gattii* *Cryptococcus deuterogattii* *Cryptococcus tetragattii* (*Cryptococcus decagattii*) *Cryptococcus bacillisporus*

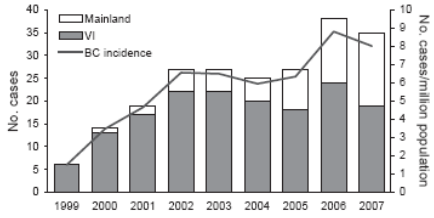
C. gattii Outbreak in Vancouver Island, Canada

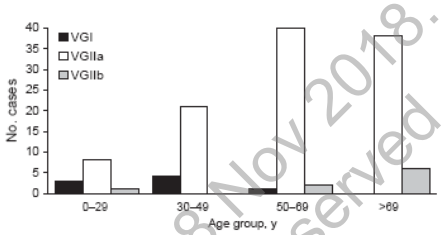


Galanis E and MacDougall L. EID 2010

C. gattii Outbreak in Vancouver Island, Canada

VGIIa subtype predominate



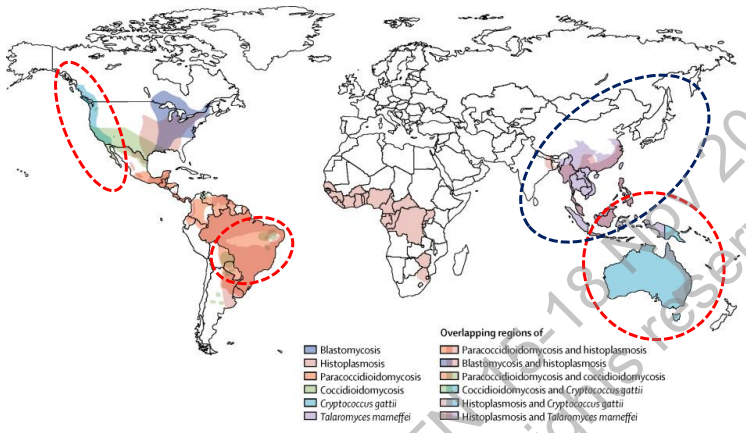


Galanis E and MacDougall L. EID 2010

The Proposed Origin of *C. gattii* Outbreak

Nature Reviews Microbiology 3, 910

Distribution of *Cryptococcus gattii* Infection



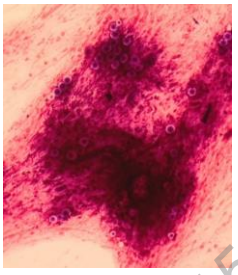
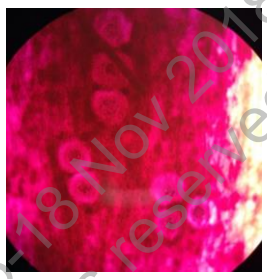
Lancet Neurol 2018; 17: 362–72

Clinical Characteristics of Cryptococcosis

	C. neoformans	*C. gattii*
Host (mainly in)	Immunocompromised	Immunocompetent
Organ involvement	CNS > Lungs	Lungs > CNS
Complications • Cryptococcoma • Hydrocephalus • Large lesion	Less	More
Antifungal susceptibility	More susceptible to fluconazole	Less susceptible to fluconazole
Treatment response	Good	Required more surgical intervention and prolonged antifungal treatment

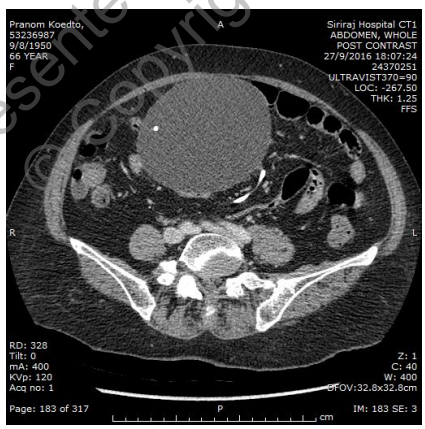
- Clin Microbiol Rev 2014;27(4):980-1024., IDSA guideline 2010 for cryptococcosis
- Clin Infect Dis 1995;21(1):28-34, Braz J Mcrobiol 2015;46(4):1125–33

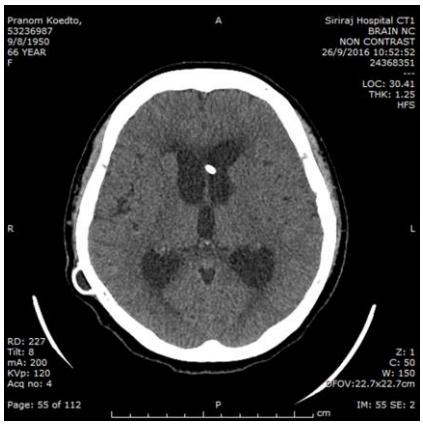
Pulmonary Cryptococcosis in A Non-HIV Patient

C. gattii molecular type VGII

Cryptococcosis in a 66-year-old non-HIV Man





C. gattii molecular type VGI

A Woman Post-Tsunami Hit

- A 48-year-old woman hit by tsunami while walking on the beach on Lanta island
- A very small puncture wound was found over the left shin in which got worse after 2 weeks of antibacterial treatment
- Culture was sent and grew *C. gattii*, molecular type VGII

Post treatment

Cutaneous cryptococcosis

Leechawengwongs M, et al. Medical Mycology Case Reports 2014;6:31–33

Association between anti-granulocyte-macrophage colony stimulating factor (anti-GM-CSF) and non-HIV cryptococcosis

Characteristics	Anti-GM-CSF positive (n=7)	Anti-GM-CSF negative (n=7)	P-value
Age(year), mean ± SD	54±8.32	66±14.71	0.084
Male, N (%)	4 (57.1%)	2 (28.6%)	0.592
Autoimmune diseases	0	2	0.462
Hypertension	5	4	1.00
Solid malignancies	0	2	0.462
Chronic kidney disease	0	2	0.462
Cryptococcosis:			
Disseminated infection	6	1	0.029
CNS	7	3	0.07
Blood stream	0	1	1.00
Pulmonary	5	3	0.592
Skin and soft tissue	1	0	1.0
Death	2 (28.6%)	3 (42.9)	1.0
IFN- γ autoantibody	0	0	NA
CD4 (%), Mean	33.9 (25.1 – 46.7)	32.2 (28.6 – 42.1)	0.482
CD8 (%), Mean	21.9 (8.6 - 40.2)	17.7 (11.4 – 22.2)	0.180

Anti-AM-CSF positive:
4/4 – *C. gattii*

Anti-GM-CSF negative:
2/3 *C. gattii*
1/3 *C. neoformans*

Chayakulkeeree M, et al. ongoing research

Diagnosis

- India ink preparation
- Staining: Gram, Wright
- Culture
- Cryptococcal antigen
  - Serum and CSF
  - Sensitivity 93-100 % and specificity 93-98%

Treatment of *C. gattii* infection

- Same as *C. neoformans* infection – lack of study in *C. gattii*
- Tend to have high fluconazole MIC (resistant to fluconazole)
  - Preferred longer induction therapy e.g. AMB+ 5-FC for 6 weeks
  - May need to use voricoanzole or posaconzole for consolidation and maintenance therapy for 6 months
- Tend to have neurological deficit and cryptococcomas
  - Early ventriculostomy or VP shunt

Clin Infect Dis 2010;50. Clin Infect Dis 2013;57(4):543-51. Lancet Infect Dis 2015;15(3):348-55.

Thank You