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## Emerging and Re-Emerging Infectious Diseases Series:

# FUNGAL DISEASES

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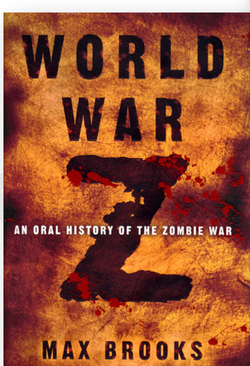
Senior Principal Scientist
Scientific Affairs

## Is Seeing the Crumbs for the Clues They Are…



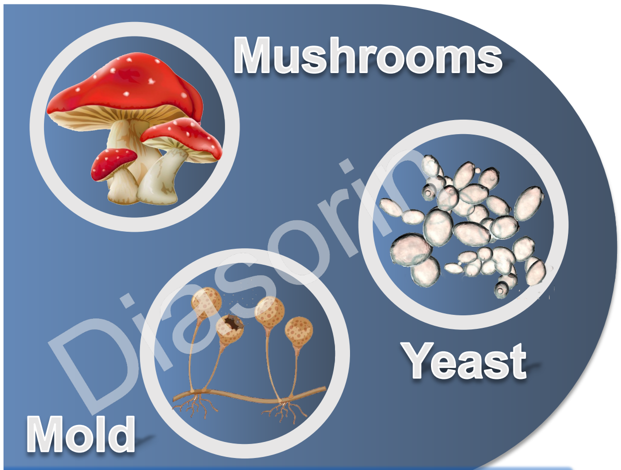


*"Mother Nature is a serial killer.*
*No ones better.*
*More creative.*

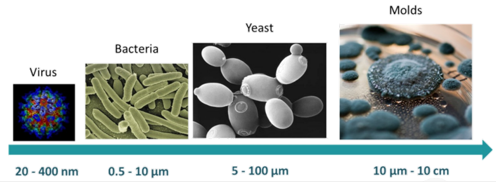
*Like all serial killers, she can't help but the urge to get caught. What good are all those brilliant crimes if nobody takes the credit? So she leaves crumbs. Now, the hard part is, and why you spend decades in school, is seeing the crumbs for the clues they are…"*

# The Kingdom Fungi

**Fungi are multicellular, eukaryotic organisms that are ubiquitous in the environment and body**




**Fungi are more closely related to humans than plants**




**5.1** million fungal species on planet Earth

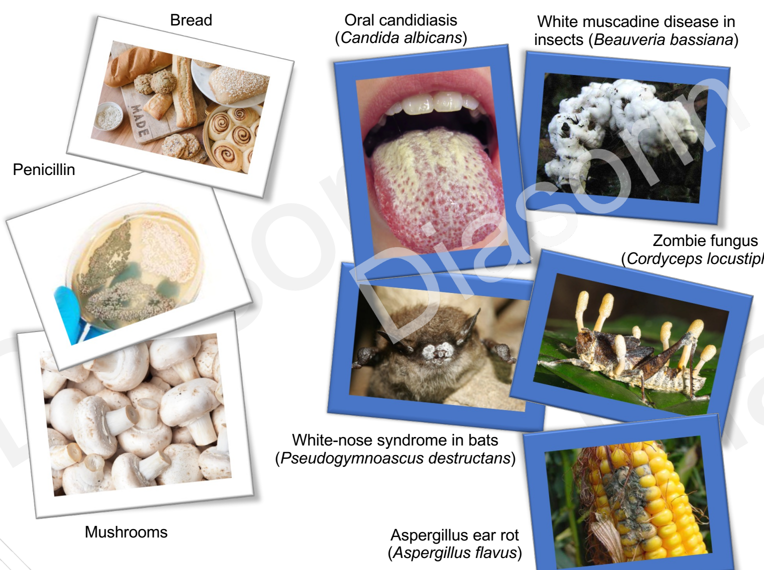
- Decomposers
- Food
- Microbiota

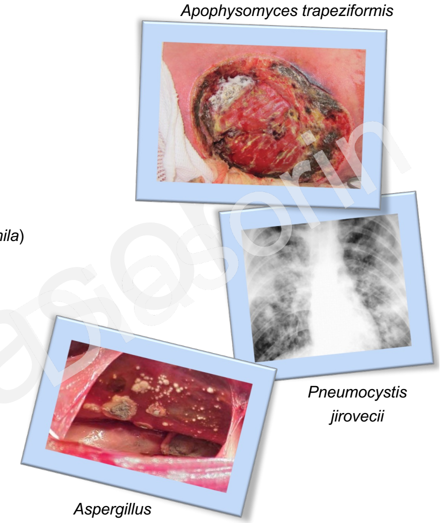
~300 species cause disease


- O'Brien, B. L., J. L. Parrent, J. A. Jackson, J. M. Moncalvo, and R. Vilgalys. 2005. Fungal community analysis by large-scale sequencing of enviromental samples. *Applied and Environmental Microbiology* 71: 5544–5550.
- Gordon D. Brown et al. ,Tackling Human Fungal Infections.Science336,647-647(2012).DOI:10.1126/science.1222236




# Fungi: The Good, the Bad, and the Ugly





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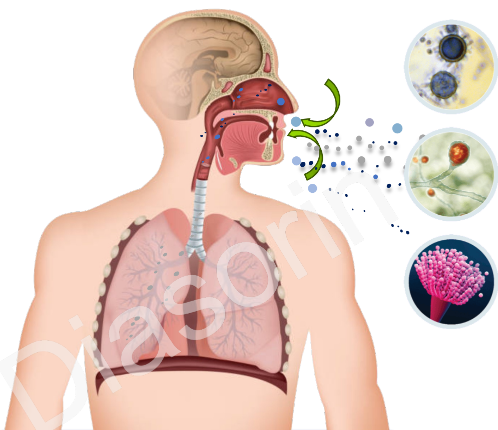
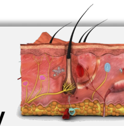
- Fisher MC, Hawkins NJ, Sanglard D, Gurr SJ. Worldwide emergence of resistance to antifungal drugs challenges health food and security. Science. 2018;360(80):739–42.
- https://www.who.int/publications/i/item/9789240060241
- Benedict K, Richardson M, Vallabhaneni S, Jackson BR, Chiller T. Emerging issues, challenges, and changing epidemiology of fungal disease outbreaks. Lancet Infect Dis. 2017 Dec;17(12):e403-e411. doi: 10.1016/S1473-3099(17)30443-7. Epub 2017 Jul 31. PMID: 28774697; PMCID: PMC5712439.

# Control of Fungal Infections in the Human Host

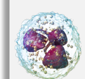


**Humans inhale between 1,000 and 10 billion spores daily**

<u>Host Factors:</u>



- **Body Internal Temperature (37℃)**
- **Cutaneous Barriers and Skin Immunity**
  - Fungal growth is discouraged by the intact skin and factors such as:
    - Naturally occurring fatty acids and derivatives act as antifungal agents
    - pH competition with the normal bacterial flora
    - Epithelial turnover rate
    - The desiccated nature of the stratum corneum
    - Mucous membranes (epithelium) contain antimicrobial proteins and peptides (AMPs)

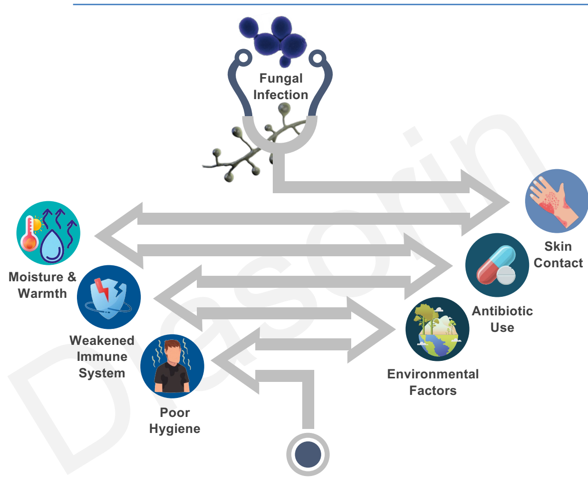


- **Immune response (by immune cells or antibodies)**
  - Cell-mediated immunity, phagocytosis, and inflammation
  - Long-term immunity (antigen-specific T cells and antibodies)

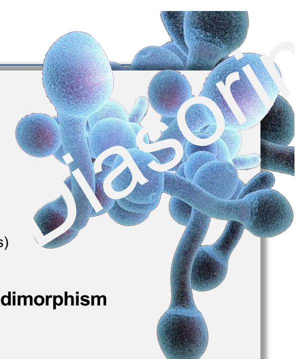

- Guimarães A, Venâncio A. The Potential of Fatty Acids and Their Derivatives as Antifungal Agents: A Review. Toxins (Basel). 2022 Mar 3;14(3):188. doi: 10.3390/toxins14030188. PMID: 35324685; PMCID: PMC8954725.
- Kobayashi GS. Disease Mechanisms of Fungi. In: Baron S, editor. Medical Microbiology. 4th edition. Galveston (TX): University of Texas Medical Branch at Galveston; 1996. Chapter 74.
- Zhang H, Zhu A. Emerging Invasive Fungal Infections: Clinical Features and Controversies in Diagnosis and Treatment Processes. Infect Drug Resist. 2020 Feb 20;13:607-615. doi: 10.2147/IDR.S237815. PMID: 32110071; PMCID: PMC7039084.
- Lionakis MS, Levitz SM. Host Control of Fungal Infections: Lessons from Basic Studies and Human Cohorts. Annu Rev Immunol. 2018 Apr 26;36:157-191. doi: 10.1146/annurev-immunol-042617-053318. Epub 2017 Dec 13. PMID: 29237128



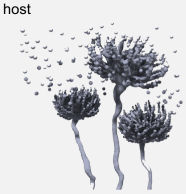

# Disease Mechanisms of Fungi




<u>Fungal Factors:</u>



- **Robustness/ stress resistance**
  - •37℃ survival
  - •Cell wall
  - •Detoxification
  - •Adaptation to niches
- **Immune evasion**
  - •Masking of PAMPs (capsule, pigments)
  - •Escape from immune cells
- **Morphological transition/thermal dimorphism**
  - •Yeast ↔ Hypha
  - •Spore ↔ Yeast
  - •Spore ↔ Hypha
  - •Molds at 30°C and as yeast at 37°C
- **Competitive metabolism**
  - Consuming energy and nutrients intended for the host
- **Adhesion/invasion**
  - •Biofilm formation
  - •Translocation
- **Damage**
  - •Hydrolytic enzymes
  - •Inflammatory stimulants
  - •Toxic metabolites



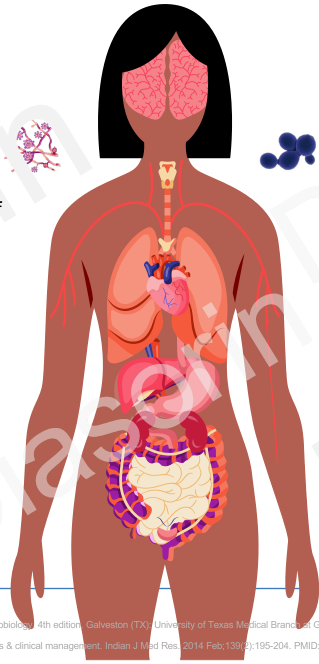

- Kobayashi GS. Disease Mechanisms of Fungi. In: Baron S, editor. Medical Microbiology. 4th edition. Galveston (TX): University of Texas Medical Branch at Galveston; 1996. Chapter 74.
- Brunke S, Mogavero S, Kasper L, Hube B. Virulence factors in fungal pathogens of man. Curr Opin Microbiol. 2016 Aug;32:89-95. doi: 10.1016/j.mib.2016.05.010. Epub 2016 May 31. PMID: 27257746.

# Fungi as Infectious Agents

## Primary Infection

Causes disease in **immunocompetent hosts** (rare, <25%)

- Infections usually result from the **inhalation** of **fungal spores** (environmental exposure)
- Infections usually **progress slowly**
- The primary manifestation of infection is **pneumonia**
  - Disseminated mycoses with pneumonia and fungemia are rare
- Usually **asymptomatic**, but asthma-like symptoms can occur
- Restricted to endemic regions



## Opportunistic Infection

Infection only in the **immunocompromised hosts** (~75%)

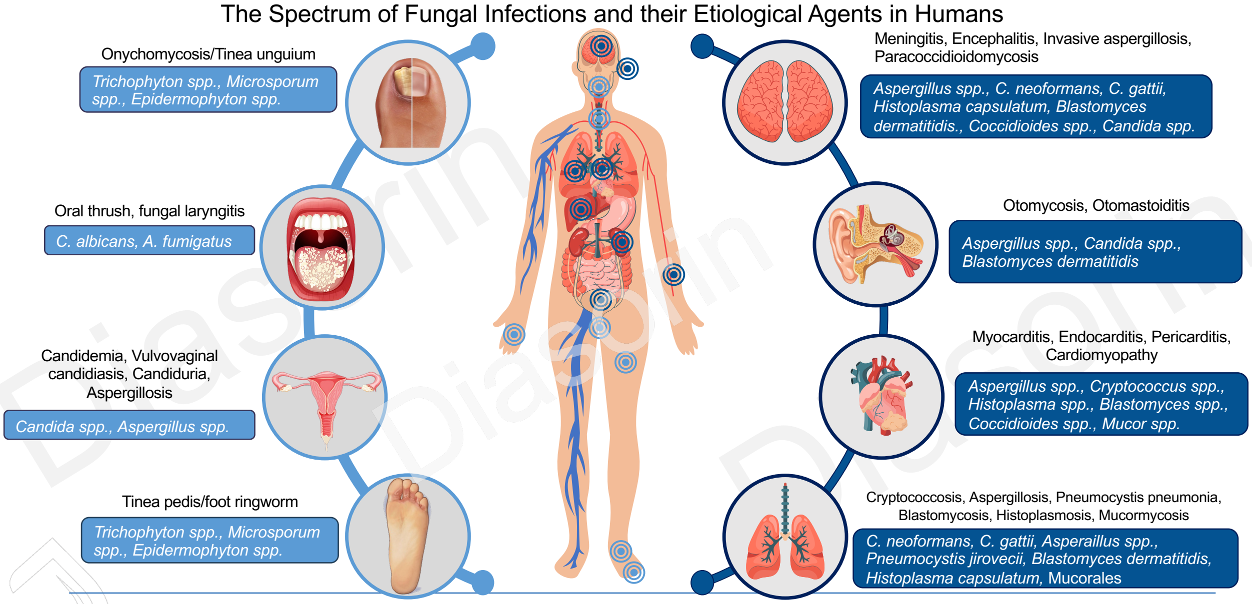
- Infections usually result due to **medical procedures, underlying disorders, undernutrition, drugs, severe burns, or a combination**
- Infections can be very **aggressive**, spreading quickly to other organs and **often leading to death**
- Often manifest in **pneumonia, fungemia, or manifestations of extrapulmonary dissemination**
- **Symptomatic**, fever, chills, inflammatory response
- Distributed worldwide


- Walsh TJ, Dixon DM. Spectrum of Mycoses. In: Baron S, editor. Medical Microbiology. 4th edition. Galveston (TX): University of Texas Medical Branch at Galveston; 1996. Chapter 75. Available from: https://www.ncbi.nlm.nih.gov/books/NBK7902/
- Badiee P, Hashemizadeh Z. Opportunistic invasive fungal infections: diagnosis & clinical management. Indian J Med Res. 2014 Feb;139(2):195-204. PMID: 24718393; PMCID: PMC4001330.




# The Spectrum of Fungal Infections

The Spectrum of Fungal Infections and their Etiological Agents in Humans



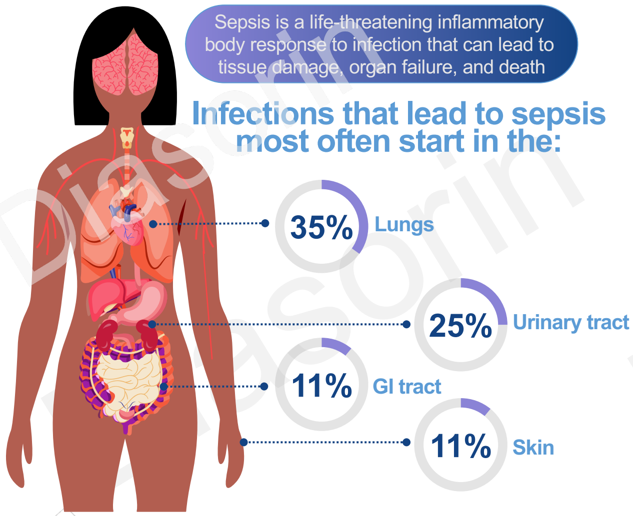


- Reddy GKK, Padmavathi AR, Nancharaiah YV. Fungal infections: Pathogenesis, antifungals and alternate treatment approaches. Curr Res Microb Sci. 2022 Apr 27;3:100137. doi: 10.1016/j.crmicr.2022.100137. PMID: 35909631; PMCID: PMC9325902.

# Invasive Fungal Infections Can Lead to Sepsis

Sepsis is a life-threatening inflammatory body response to infection that can lead to tissue damage, organ failure, and death

**Infections that lead to sepsis most often start in the:**




- **~17% of sepsis** can be attributed to ***Candida* species**, with **2–3%** more caused by ***Aspergillus*** and **other fungi**
- Fungal sepsis is almost exclusively acquired in a healthcare setting
  - **93%** of bloodstream candidiasis is **hospital-acquired**
  - **>80%** of patients exposed to **empiric antibiotics**

**Most people recover from mild fungal sepsis, but the mortality rate for septic shock is**
**40-60%**

Fungal sepsis has a **Higher** case-fatality rate than bacterial or viral sepsis (~30%)


- Delaloye J, Calandra T. Invasive candidiasis as a cause of sepsis in the critically ill patient. Virulence. 2014 Jan 1;5(1):161-9. doi: 10.4161/viru.26187. Epub 2013 Aug 27. PMID: 24157707; PMCID: PMC3916370.
- Kollef M, Micek S, Hampton N, Doherty JA, Kumar A. Septic shock attributed to Candida infection: importance of empiric therapy and source control. Clin Infect Dis. 2012;54:1739–46
- Dolin HH, Papadimos TJ, Chen X, Pan ZK. Characterization of Pathogenic Sepsis Etiologies and Patient Profiles: A Novel Approach to Triage and Treatment. Microbiol Insights. 2019 Jan 27;12:1178636118825081. doi: 10.1177/1178636118825081. PMID: 30728724; PMCID: PMC6350122.
- https://www.cdc.gov/sepsis/




# The Kingdom Fungi: A Global Health Threat

Opportunistic

Hospital-associated

Community-acquired

**150 million** of severe cases per year of fungal infections occur worldwide

**3.7 million** is the number of people per year fungal diseases kill

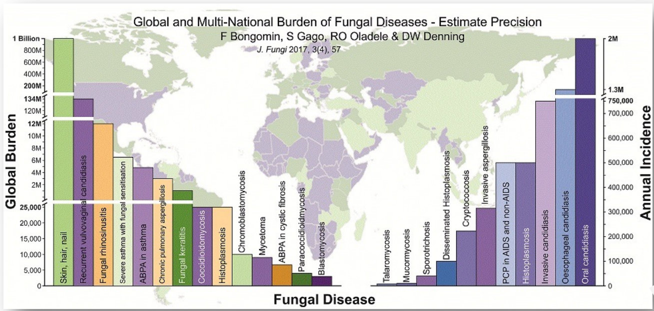
**118%↑ (2017)**

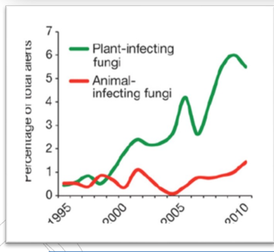
- Approximately **15% of healthcare-associated** infections are caused by fungi
- Fungal infection of the skin, hair, or nails affects **~1 billion people worldwide**
- In the US:

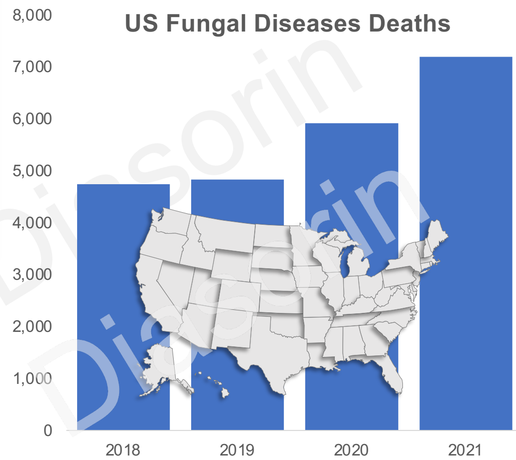
  - **9 MILLION -** annual outpatient visits
  - **75,000 -** annual hospitalizations
  - Direct medical costs are estimated at **$6.7 to $7.5 billion** yearly


- O'Brien HE, Parrent JL, Jackson JA, Moncalvo JM, Vilgalys R 2005. Fungal community analysis by large-scale sequencing of environmental samples. Appl Environ Microbiol 71: 5544–5550.
- Denning DW, Perlin DS, Muldoon EG, et al. Delivering on Antimicrobial Resistance Agenda Not Possible without Improving Fungal Diagnostic Capabilities. Emerging Infectious Diseases. 2017;23(2):177-183
- Fisher MC, Hawkins NJ, Sanglard D, Gurr SJ. Worldwide emergence of resistance to antifungal drugs challenges health food and security. Science. 2018;360(80):739–42.
- https://www.cdc.gov/fungal/about-fungal-diseases.html
- Benedict K, Jackson BR, Chiller T, Beer KD. Estimation of direct healthcare costs of fungal diseases in the United States. Clin Infect Dis. 2019 May 17.
- Delaloye J, Calandra T. Invasive candidiasis as a cause of sepsis in the critically ill patient. Virulence. 2014 Jan 1;5(1):161-9. doi: 10.4161/viru.26187. Epub 2013 Aug 27. PMID: 24157707; PMCID: PMC3916370.
- Kainz K, Bauer MA, Madeo F, Carmona-Gutierrez D. Fungal infections in humans: the silent crisis. Microb Cell. 2020 Jun 1;7(6):143-145. doi: 10.15698/mic2020.06.718. PMID: 32548176; PMCID: PMC7278517.

## Fungal Diseases Are on the Rise



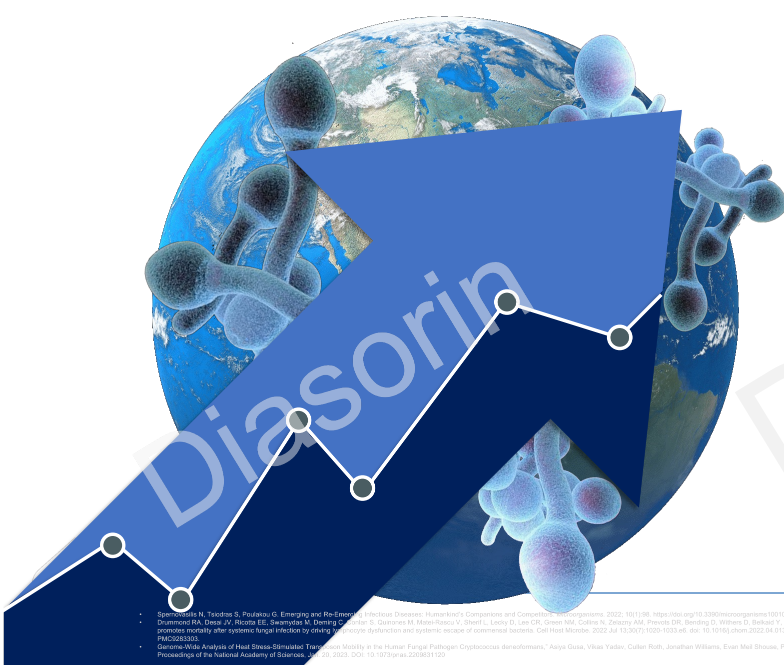




Source: CDC

- https://www.cdc.gov/fungal/cdc-and-fungal/burden.html
- Denning DW. Global incidence and mortality of severe fungal disease. Lancet Infect Dis. Published online January 12, 2024. doi:10.1016/S1473-3099(23)00692-8
- Bongomin F, Gago S, Oladele RO, Denning DW. Global and Multi-National Prevalence of Fungal Diseases-Estimate Precision. J Fungi (Basel). 2017;3(4):57. Published 2017 Oct 18. doi:10.3390/jof3040057
- https://ensia.com/features/19036/



## Factors Contributing to the Emergence and Re-emergence of Fungal Infections



### Immunosuppression, modern medicine, and accessibility to therapies

Fungal diseases are flourishing in newly susceptible populations

### Links to Climate Change

New fungal diseases may emerge as fungi evolve to survive in warmer conditions, potentially aiding their ability to infect humans. Extreme weather events lead to an increase in their geographical range.

### Drug Resistance

Increasing resistance is associated with inappropriate use of antifungal agents in humans, animals, and agriculture

### Overuse of antibiotics

Microbiome imbalance

- Spernovasilis N, Tsiodras S, Poulakou G. Emerging and Re-Emerging Infectious Diseases: Humankind's Companions and Competitors. *Microorganisms*. 2022; 10(1):98. https://doi.org/10.3390/microorganisms10010098
- Drummond RA, Desai JV, Ricotta EE, Swamydas M, Deming C, Conlan S, Quinones M, Matei-Rascu V, Sherif L, Lecky D, Lee CR, Green NM, Collins N, Zelazny AM, Prevots DR, Bending D, Withers D, Belkaid Y, Segre JA, Lionakis MS. Long-term antibiotic exposure promotes mortality after systemic fungal infection by driving lymphocyte dysfunction and systemic escape of commensal bacteria. Cell Host Microbe. 2022 Jul 13;30(7):1020-1033.e6. doi: 10.1016/j.chom.2022.04.013. Epub 2022 May 13. PMID: 35568028; PMCID: PMC9283303.
- Genome-Wide Analysis of Heat Stress-Stimulated Transposon Mobility in the Human Fungal Pathogen Cryptococcus deneoformans," Asiya Gusa, Vikas Yadav, Cullen Roth, Jonathan Williams, Evan Meil Shouse, Paul Magwene, Joseph Heitman, Sue Jinks-Robertson. Proceedings of the National Academy of Sciences, Jan. 20, 2023. DOI: 10.1073/pnas.2209831120

# Antimicrobial-Resistant Fungi

*Aspergillus*

**~19%**

of *A. fumigatus* infections are resistant to azole antifungals

*Candida*

**~7%**

of bloodstream infections are resistant to antifungals

*Candida auris*

**~90%**

of cases are resistant to at least one antifungal

Ringworm

**%?**

estimate in the US is unknown


- https://www.cdc.gov/fungal/antifungal-resistance.html#:~:text=Fungi%20can%20develop%20resistance%20to,killed%20and%20continue%20to%20grow.
- Lestrade PP, Bentvelsen RG, Schauwvlieghe AFAD, Sch 452 alekamp S, van der Velden WJFM, Kuiper EJ, et al. 2019. Voriconazole Resistance and Mortality in Invasive Aspergillosis: A Multicenter Retrospective Cohort Study. Clin Infect Dis 68:1463–1471; doi:10.1093/cid/ciy859.




# Antifungal Resistance in Superficial Mycoses

tinea corporis

tinea cruris

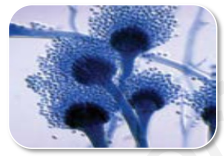
- An epidemic-like spread of **recalcitrant** and **terbinafine-resistant** dermatophytosis (*Trichophyton spp.*) has been reported across South Asia since 2015 (up to 71%)
- In recent years, 85% of European countries have also reported clinical and/or mycological confirmation of terbinafine-resistant dermatophytosis
  - **First Reported US Cases of Tinea Caused by *Trichophyton indotineae* — New York City, December 2021–March 2023**
- What factors might be contributing to the emergence and spread of antimicrobial-resistant dermatophytes?
  - Overuse of over-the-counter topical antifungal creams
  - Inappropriate use of topical steroid creams
  - Inappropriate prescription of antifungal drugs
  - Inadequate adherence to prescribed courses of antifungal medication
  - Global travel and migration


- Gupta AK, Renaud HJ, Quinlan EM, Shear NH, Piguet V. The Growing Problem of Antifungal Resistance in Onychomycosis and Other Superficial Mycoses. Am J Clin Dermatol. 2021 Mar;22(2):149-157. doi: 10.1007/s40257-020-00580-6. Epub 2020 Dec 22. PMID: 33354740.
- Cañete-Gibas CF, Mele J, Patterson HP, Sanders CJ, Ferrer D, Garcia V, Fan H, David M, Wiederhold NP. Terbinafine-Resistant Dermatophytes and the Presence of Trichophyton indotineae in North America. J Clin Microbiol. 2023 Jul 11:e0056223. doi: 10.1128/jcm.00562-23. Epub ahead of print. PMID: 37432126.
- https://www.cdc.gov/fungal/diseases/ringworm/dermatophyte-resistance.html
- Caplan AS, Chaturvedi S, Zhu Y, et al. Notes from the Field: First Reported U.S. Cases of Tinea Caused by Trichophyton indotineae — New York City, December 2021–March 2023. MMWR Morb Mortal Wkly Rep 2023;72:536–537.

# Emerging and Re-Emerging Fungal Pathogens

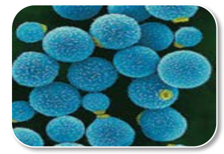
*Candida auris*

More than **90%** of all reported fungal-related deaths result from ***Cryptococcus***, ***Candida***, ***Aspergillus***, ***Histoplasma***, and ***Pneumocystis.***



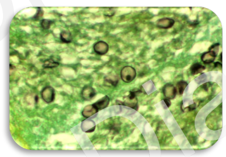
***Aspergillus spp.***

*A. fumigatus, A. niger, A. flavius, A. terreus*

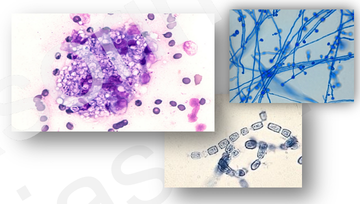


***Cryptococcus***

*C. neoformans, C. gattii*



***Pneumocystis jirovecii***



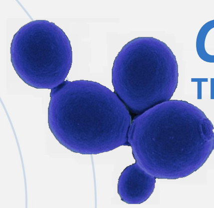
**Dimorphic fungi**

*Histoplasma, Coccidioides, Blastomyces*


- Fisher MC, Hawkins NJ, Sanglard D, Gurr SJ. Worldwide emergence of resistance to antifungal drugs challenges health food and security. Science. 2018;360(80):739–42.
- https://www.who.int/publications/i/item/9789240060241
- Brown GD, Denning DW, Gow NA, et al.. Hidden killers: human fungal infections. Sci Transl Med 2012; 4:165rv13.
- Adenis AA, Valdes A, Cropet C, et al.. Burden of HIV-associated histoplasmosis compared with tuberculosis in Latin America: a modelling study. Lancet Infect Dis 2018; 18:1150–9





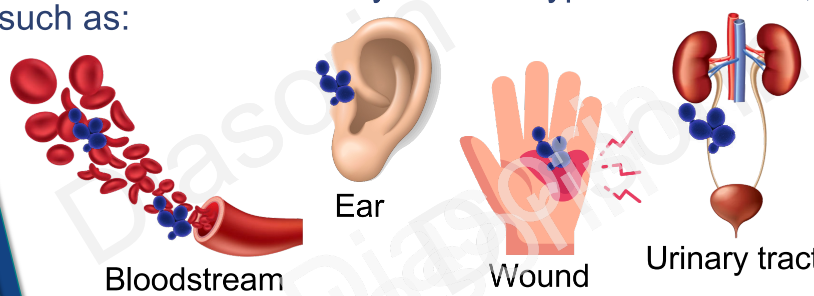



# *Candida auris*

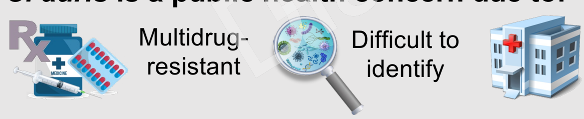
## The Rise of a Fungal Superbug

## General Overview


- *C. auris* is an emerging **multidrug-resistant (MDR)** fungus that presents a serious global health threat
- *C. auris* can cause many different types of infection, such as:




***C. auris* is a public health concern due to:**





Emily S. Spivak, Kimberly E. Hanson. Candida auris: an Emerging Fungal Pathogen. Journal of Clinical Microbiology Jan 2018, 56 (2) e01588-17; DOI: 10.1128/JCM.01588-17




## Epidemiology

# 1 of the top 18

**antimicrobial-resistant threats in the US**

**Total cases in the USA have climbed to a nearly 400% increase in just four years (2018-2022)**

**>$1,000,000**

of direct medical costs of healthcare-associated infections in US hospitals

**Resistance to all three of the main classes of antifungal drugs**

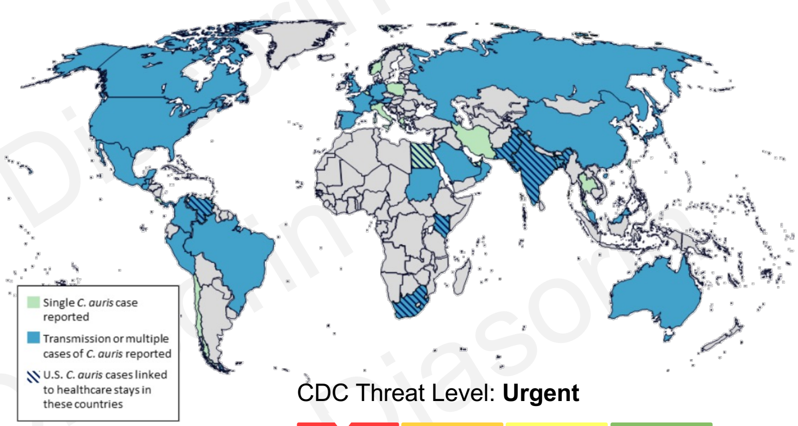
**90%** of cases are resistant to at least **one**

**30%** of cases are resistant to **two or more**

**50%** of clinical cases are bloodstream infections

**30-60%** mortality rate among hospitalized patients

### Worldwide distribution of *C. auris* reported cases



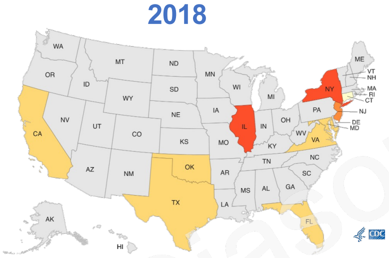

CDC Threat Level: **Urgent**


- Source: Centers for Disease Control and Prevention, National Center for Emerging and Zoonotic infectious Diseases (NCEZID), Division of Foodborne, Waterborne, and Environmental Diseases (DFWED)
- Cortegiani, A., Misseri, G., Fasciana, T. et al. Epidemiology, clinical characteristics, resistance, and treatment of infections by Candida auris. j intensive care 6, 69 (2018)
- Magill SS, Edwards JR, Bamberg W, Beldavs ZG, Dumyati G, Kainer MA, et al. Multistate point-prevalence survey of health care-associated infectionsexternal icon. N Engl J Med. 2014 Mar 27

# Cases of *C. auris* Reported in the US

**Number of *C. auris* Clinical Cases by State (January – December)**

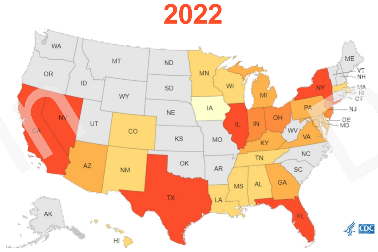
**2018**



**Confirmed Clinical Cases: 331**

**Screening Cases: 696**

**2022**



**Confirmed Clinical Cases: 2,377**

**Screening Cases: 5,754**

- 0 clincial cases and at least 1 screening case
- 11 to 50
- 101 to 500
- 1001 or more
- 1 to 10
- 51 to 100
- 501 to 1000

Prevalence ranging from

**5 - 30%**

of **all *Candida*** cases in certain states

**Pan-resist... outbreaks identified in the US in 2021**


https://www.cdc.gov/fungal/candida-auris/tracking-c-auris.html Accessed 9/10/2021
Rudramurthy SM, Chakrabarti A, Paul RA, Sood P, Kaur H, Capoor MR, et al. Candida auris candidaemia in Indian ICUs: analysis of risk factors. J Antimicrob Chemother. 2017;72:1794–801.; Jeffery-Smith A, Taori SK, Schelenz S, et al. Candida auris: a Review of the Literature. Clin Microbiol Rev. 2017;31(1):e00029-17. Published 2017 Nov 15.; https://www.cidrap.umn.edu/news-perspective/2021/07/cdc-reports-two-outbreaks-pan-resistant-candida-auris



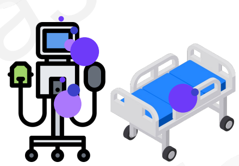
# *C. auris*, the "Lurking Scourge"

It can persist on environmental surfaces (**up to 3 months**), and common disinfectants are not effective


HOSPITALS

**TRANSMISSION**

HUMAN CONTACT



CONTAMINATED OBJECTS


- Blood-pressure cuffs
- Stethoscopes
- Ventilators
- Over-bed tables
- Bedside chairs
- Nursing carts
- Doorknobs
- Bedrails
- Windowsills

- Cortegiani, A., Misseri, G., Fasciana, T. et al. Epidemiology, clinical characteristics, resistance, and treatment of infections by Candida auris. j intensive care 6, 69 (2018).
- Source: https://www.longbeach.gov/globalassets/health/media-library/documents/diseases-and-condition/resources-for-providers/candida-auris/lb-health-c--auris-info-sesstion-8-7-19. CA Dept of Public Health, Presented 6/24/19
- Pacilli, .M., Kerins, J.L., Clegg, W.J., Walblay, K.A., Adil, .H., Kemble, S.K., Xydis, .S., McPherson, T.D., Lin, M.Y., Hayden, M.K., Froilan, M.C., Soda, .E., Tang, A.S., Valley, .A., Forsberg, .K., Gable, .P., Moulton-Meissner, .H., Sexton, D.J., Jacobs Slifka, K.M., Vallabhaneni, .S., Walters, M.S., & Black, S.R. (2020). Regional Emergence of Candida auris in Chicago and Lessons Learned From Intensive Follow-up at 1 Ventilator-Capable Skilled Nursing Facility. Clinical Infectious Diseases, 71(11), e718-e725.

# Laboratory Identification of *C. auris*

## Phenotypic Identification (culture-based)

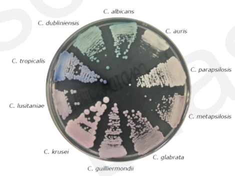
**Needed for antifungal susceptibility testing**

**Sabouraud Dextrose Agar**

- Takes up to 72 hours to grow *C. auris* + has specificity issues

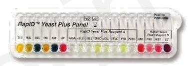
**CHROMagar™ Candida+**

- Presumptive test
- It takes 48 hrs to see colonies on plates and another 24hrs to see coloration (~72 hrs)
- Pigments may cause inhibition of MALDI or PCR




## Biochemical identification

- Screening test
- Specificity issues (*C. auris/C. haemulonii* complex)




## Proteomic-based method

**MALDI-TOF MS**

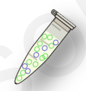
- Accurate identification
- Reading takes ~20 min
- High-throughput
- It takes up to 72 hrs to grow *C. auris* before MALDI-TOF analysis
- High-cost equipment
- The extraction method can influence the results (direct smear, full, or partial extraction)


## Molecular-based methods

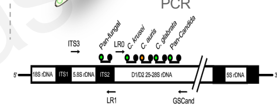
**PCR or sequencing**

- Accurate identification
- Faster TAT
- Isolates are not required for testing
- Limited FDA-cleared assays + claims
- Fungal extraction can be tedious

PCR-BASED METHODS



- End-point PCR
- PCR - RFLP
- LAMP
- Real-Time PCR



rDNA SEQUENCING

- Keighley, C., Garnham, K., Harch, S.A.J. *et al. Candida auris:* Diagnostic Challenges and Emerging Opportunities for the Clinical Microbiology Laboratory. *Curr Fungal Infect Rep* **15**, 116–126 (2021). https://doi.org/10.1007/s12281-021-00420-y



# *C. auris* Colonization (Asymptomatic) Screening

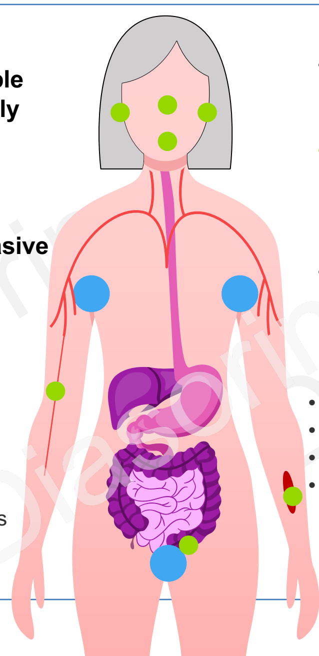
## Why is it important?

1. **Asymptomatic colonizers shed viable yeast cells from their skin continuously**
   - Source for patients or environmental transmission

2. **Colonization is a risk factor for invasive infection**

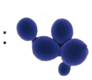
| **~30%** | **1 in 3** |
|---|---|
| of colonized patients will develop an infection | will die from complications |

3. **No currently known decolonization strategies**
   - Patients can remain colonized for weeks to months (continuous source of transmission)



## How to screen?

- Most common and recommended by CDC: **bilateral axilla and groin**
- **Less common**:



  - Nose
  - Mouth
  - External ear canals
  - Rectum
  - Wounds
  - Urine
- Disseminated cases:
  - Blood

## When to screen?

- Suspected exposure (contact tracing)
- Admission screening from high-risk facilities
- History of healthcare abroad
- Suspected colonization or infection with Carbapenemase Producing Organisms (CPO)

https://www.cdc.gov/fungal/candida-auris/c-auris-screening.html

# *C.auris*'s Ability to Colonize Multiple Body Sites

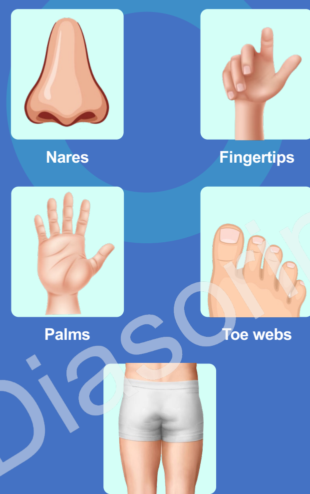
**DP**

**Integrated genomic, epidemiologic investigation of *C.auris* skin colonization**

- Frequency of colonization: **nares (42.9%), palms/fingertips (40.4%),** and **toe webs (35.7%)**
- Most colonized residents (69.6%) were colonized at two or more sites
- Single sites have **lower sensitivity**
- Current screening recommendations identify 79.7% of *C. auris* carriers

Proctor, Diana M et al. 2021

**Other body sites**




**SS**

**Rapid Environmental Contamination With *C. auris***

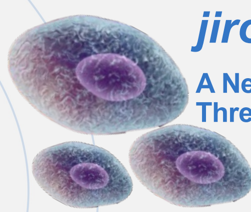
- 41 known *C. auris* carriers, colonization was detected most frequently on **palms/fingertips (76%)** and **nares (71%)**
- Detected less often on **perianal skin (54%), axillae (56%),** and **inguinal creases (56%)**
- Current screening recommendations identify 83% of *C. auris* carriers

Sansom, Sarah E et al. 2023


- Huang X, Welsh RM, Deming C, Proctor DM, Thomas PJ, Gussin GM, et al. Skin Metagenomic Sequence Analysis of Early Candida auris Outbreaks in U.S. Nursing Homes. mSphere. 2021;6(4):e0028721. Epub 2021/08/05. doi: 10.1128/mSphere.00287-21 ; PubMed Central PMCID: PMC8386442
- Eix EF, Nett JE. Modeling Candida auris skin colonization: Mice, swine, and humans. PLoS Pathog. 2022;18(9):e1010730. Published 2022 Sep 8. doi:10.1371/journal.ppat.1010730
- Proctor, Diana M et al. "Integrated genomic, epidemiologic investigation of Candida auris skin colonization in a skilled nursing facility." Nature medicine vol. 27,8 (2021): 1401-1409. doi:10.1038/s41591-021-01383-w
- Sansom, Sarah E et al. "Rapid Environmental Contamination with Candida auris and Multidrug-Resistant Bacterial Pathogens Near Colonized Patients." Clinical infectious diseases : an official publication of the Infectious Diseases Society of America, ciad752. 6 Dec. 2023, doi:10.1093/cid/ciad752



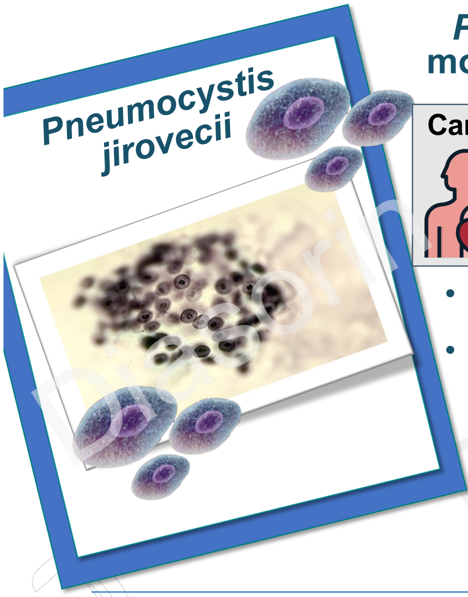


# *Pneumocystis jirovecii*

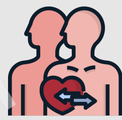
## A Neglected Emerging Growing Threat

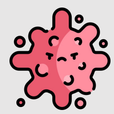
## *Pneumocystis jirovecii*




### *P. jirovecii* pneumonia is a fungal infection that most commonly affects the immunocompromised

**Can be severely life-threatening to:**


Transplant recipients

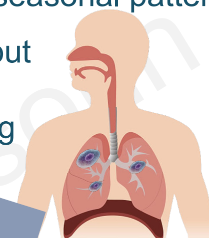

Cancer



Immunosuppressed

- Distributed worldwide; with no distinct seasonal pattern
- *P. jirovecii* primarily affects the lungs, but extrapulmonary infections result from dissemination to other organs, including the **central nervous system**, **eyes**, **GI tract**, etc.

Disease = PcP *Pneumocystis pneumonia*


**Pneumocystis Pneumonia (PcP)**

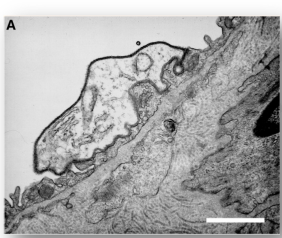
https://www.cdc.gov/fungal/diseases/pneumocystis-pneumonia/



## Fungal Biology of *Pneumocystis jirovecii*

Atypical fungus

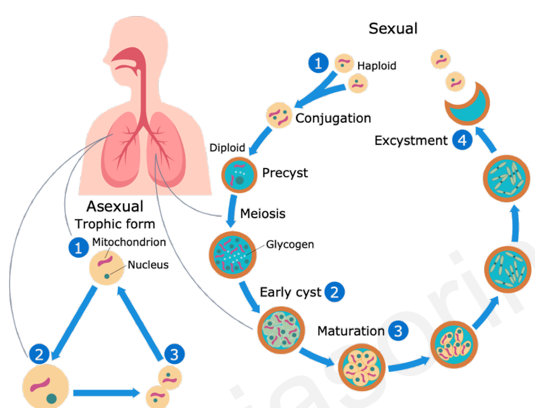
- Host-obligate pulmonary pathogen
- The cell wall contains cholesterol rather than ergosterol
  (treatment of choice Trimethoprim-Sulfamethoxazole (TMP-SMX))
- Biphasic life cycle
- It lacks virulence genes or toxins
- The organism is communicable



The trophozoite (trophic form), 1-5 µm, pleomorphic and contains a single nucleus

A thick-walled cyst, which contains several intracystic bodies (spores)

*Pneumocystis* life cycle





- Gigliotti F, Limper AH, Wright T. Pneumocystis. Cold Spring Harb Perspect Med. 2014 Nov 3;4(12):a019828. doi: 10.1101/cshperspect.a019828. PMID: 25367973; PMCID: PMC4292088.
- https://www.cdc.gov/dpdx/pneumocystis/index.html
- Ruffolo JJ. Pneumocystis carinii Cell Structure. In: Walzer, PD, editor. Pneumocystis carinii Pneumonia. 2nd ed. Marcel Dekker; 1994. p. 25-43.
- Thomas CF Jr, Limper AH. Current insights into the biology and pathogenesis of Pneumocystis pneumonia. Nat Rev Microbiol. 2007 Apr;5(4):298-308. doi: 10.1038/nrmicro1621. PMID: 17363968.
- Cushion MT, Ruffolo JJ, Walzer PD. Analysis of the developmental stages of Pneumocystis carinii in vitro. Lab Invest 1988;58:324-331.

# Epidemiology

Global estimates are as high as **500,000 annual cases**

**$475–$686 million**
of direct medical costs of healthcare-associated infections in US hospitals


| | |
|---|---|
| **HIV Patients** | **20 - 40%** |
| **Non-HIV Patients** | **30 - 50%** |

- Immunocompetent individuals (carriers)
  - Most individuals acquire the organism by 4 years of age (75%)
  - Colonization prevalence, 24% (adults), 32% to 100% (children)
- HIV positive
  - The most prevalent opportunistic infection
  - Co-infections are common (e.g., TB, CMV, etc.)
  - Colonization prevalence, as high as 68%
  - Disseminated PcP is common
- PcP in immunocompromised children
  - Up to 1–2% of cases of community-acquired pneumonia in children under 5
  - Prevalence
    - HIV-infected children in Africa have high rates of PcP (80%)
    - Children dying of sudden infant death syndrome (SIDS) also have a high rate of *Pneumocystis* (30%)


- Medrano FJ, Montes-Cano M, Conde M, de la Horra C, Respaldiza N, Gasch A, et al. Pneumocystis jirovecii in general populationexternal icon. Emerg Infect Dis 2005;11:245-50.
- Truong J, Ashurst JV. Pneumocystis Jirovecii Pneumonia. [Updated 2022 Nov 23]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from:
- https://www.ncbi.nlm.nih.gov/books/NBK482370/?report=classic
- Xue T, Kong X, Ma L. Trends in the Epidemiology of Pneumocystis Pneumonia in Immunocompromised Patients without HIV Infection. J Fungi (Basel). 2023 Jul 31;9(8):812. doi: 10.3390/jof9080812. PMID: 37623583; PMCID: PMC10455156.
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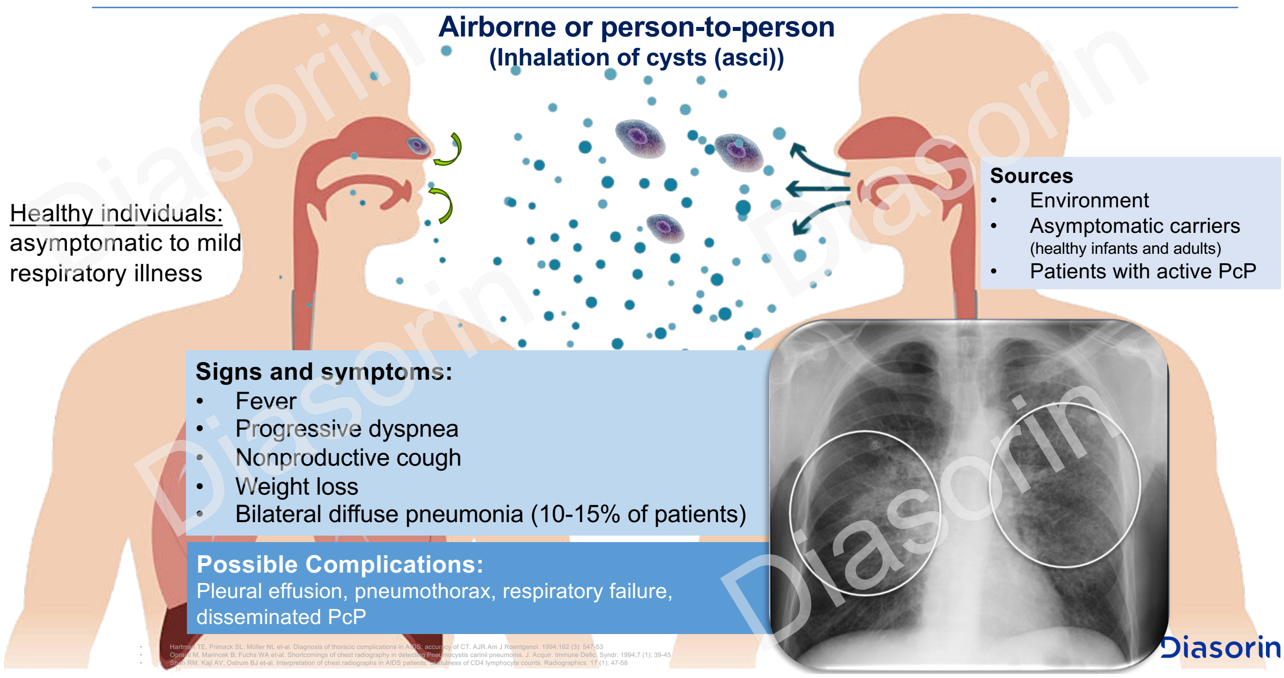
- Morris A, Lundgren JD, Masur H, Walzer PD, Hanson DL, Frederick T, Huang L, Beard CB, Kaplan JE. Current epidemiology of Pneumocystis pneumonia. Emerg Infect Dis. 2004 Oct;10(10):1713-20. doi: 10.3201/eid1010.030985. PMID: 15504255; PMCID: PMC3323247.




# Transmission and Clinical Presentation

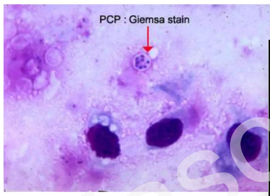




- Hartman TE, Primack SL, Müller NL et-al. Diagnosis of thoracic complications in AIDS: accuracy of CT. AJR Am J Roentgenol. 1994;162 (3): 547-53
- Opravil M, Marincek B, Fuchs WA et-al. Shortcomings of chest radiography in detecting Pneumocystis carinii pneumonia. J. Acquir. Immune Defic. Syndr. 1994;7 (1): 39-45
- Shah RM, Kaji AV, Ostrum BJ et-al. Interpretation of chest radiographs in AIDS patients: usefulness of CD4 lymphocyte counts. Radiographics. 17 (1): 47-58

# Laboratory Detection

## Traditional diagnostic tests

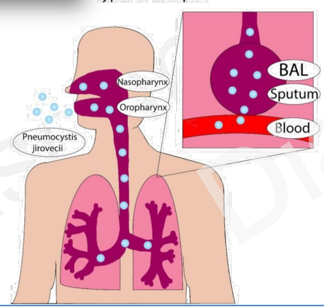



**STAINING**

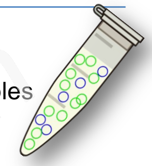
**Direct Immunofluorescence**

- Low cost
- Reliant on sample quality
- Accuracy depends on highly skilled operators
- High false negative rate (due to low fungal burden)
  - If negative, do not rule out the presence of PcP

Types of Samples




**PCR**



- High sensitivity
- It can be used on noninvasive samples
- Requires highly skilled operators
- Fast turnaround
- Moderate-high cost
- Failure to distinguish between active infection and colonization
- Not widely available

Additional novel methods of detection:

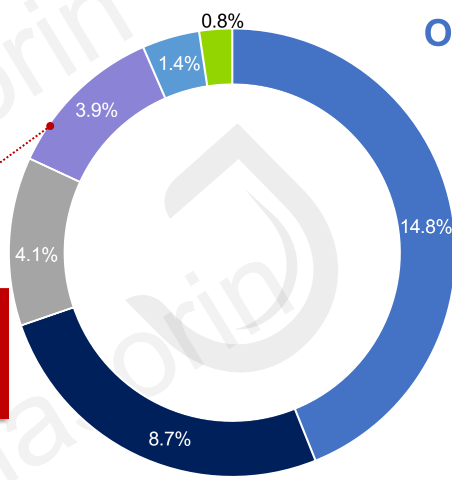
- Loop-mediated isothermal amplification (LAMP)
- Flow cytometry
- Antibody assays
- Antigen and biomarker assays


- Bateman, M., Oladele, R., & Kolls, J. K. (2020). Diagnosing Pneumocystis jirovecii pneumonia: A review of current methods and novel approaches. *Medical mycology*, *58*(8), 1015–1028. https://doi.org/10.1093/mmy/myaa024
- Melanie T Cushion, A George Smulian, and Margaret V. Powers-Fletcher , 2023. Pneumocystis jirovecii, Manual of Clinical Microbiology, 12th Edition. ASM Press, Washington, DC. doi: 10.1128/9781683670438.MCM.ch121




# Treatment Prognosis Factors for *Pneumocystis* Pneumonia

1. Co-infections




The co-infection rate was found to be 37.5% (6/16) and 35.2% (12/34) in HIV infected and non-HIV infected patients (Killic et al. 2020)

**OVERALL CO-INFECTION**

**29.3% (95% CI 25.4 - 33.6)**

- **TB** 14.8% (11.8 - 18.5)
- **Bacterial pneumonia** 8.7% (0.6 - 11.8)
- **Pulmonary Kaposi sarcoma** 4.1% (2.4 - 6.6)
- **Pulmonary CMV** 3.9% (1.4 - 8.2)
- **Pulmonary cryptococcosis** 1.4% (0.4 - 3.6)
- **Pulmonary MAC** 0.8% (0.1 – 2.8)


- Wasserman, S., Engel, M.E., Griesel, R. *et al.* Burden of pneumocystis pneumonia in HIV-infected adults in sub-Saharan Africa: a systematic review and meta-analysis. *BMC Infect Dis* **16**, 482 (2016). https://doi.org/10.1186/s12879-016-1809-3
- Kilic A, Elliott S, Hester L, Palavecino E. Evaluation of the performance of DiaSorin molecular Pneumocystis jirovecii-CMV multiplex real-time PCR assay from bronchoalveolar lavage samples. J Mycol Med. 2020 Jun;30(2):100936. doi: 10.1016/j.mycmed.2020.100936. Epub 2020 Jan 31. PMID: 32044156; PMCID: PMC7102588.

# Treatment Prognosis Factors for *Pneumocystis* Pneumonia

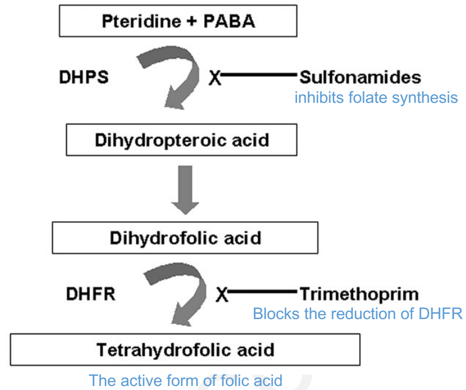
1. Co-infections
2. Resistance

**Point mutations in *P. jirovecii fas* gene**

- Encodes dihydropteroate synthase (DHPS)
  - Nonsynonymous point mutations (amino acid substitutions at positions 55, 57, or both)
- Gene has shown resistance to sulfa drugs (TMP-SMX or dapsone)
  - TMP-SMX resistance among bacteria is common (e.g., *E. coli*, *S. aureus*, *P. falciparum, Enterobacteriaceae* species, etc.)
- Factors that contribute to the presence of *P. jirovecii* harboring DHPS mutations
  - **PCP prophylaxis usage** (19%–80%)
  - **Person-to-person transmission of mutated strains** (~48%)
  - **Geographic distribution** (USA > European)

**Challenges:**

- DHPS mutation could be associated with a poor prognosis in PcP (Crothers et al. 2005)
- The inability to culture prevents routine susceptibility testing and detection of drug resistance




PABA, para-aminobenzoic acid
DHFR, dihydrofolate reductase


- Singh, Y., Mirdha, B.R., Guleria, R., Kabra, S.K., Mohan, A., Chaudhry, R., Kumar, L., Dwivedi, S.N., & Agarwal, S.K. (2019). Novel dihydropteroate synthase gene mutation in Pneumocystis jirovecii among HIV-infected patients in India: Putative association with drug resistance and mortality. Journal of global antimicrobial resistance, 17, 236-239 .
- de la Horra C, Friaza V, Morilla R, Delgado J, Medrano FJ, Miller RF, de Armas Y, Calderón EJ. Update on Dihydropteroate Synthase (DHPS) Mutations in Pneumocystis jirovecii. J Fungi (Basel). 2021 Oct 13;7(10):856. doi: 10.3390/jof7100856. PMID: 34682277; PMCID: PMC8540849.
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- Crothers K., Beard C.B., Turner J., Groner G., Fox M., Morris A., Eiser S., Huang L. Severity and outcome of HIV-associated Pneumocystis pneumonia containing Pneumocystis jirovecii dihydropteroate synthase gene mutations. AIDS. 2005;19:801–805.




# Treatment Prognosis Factors for *Pneumocystis* Pneumonia

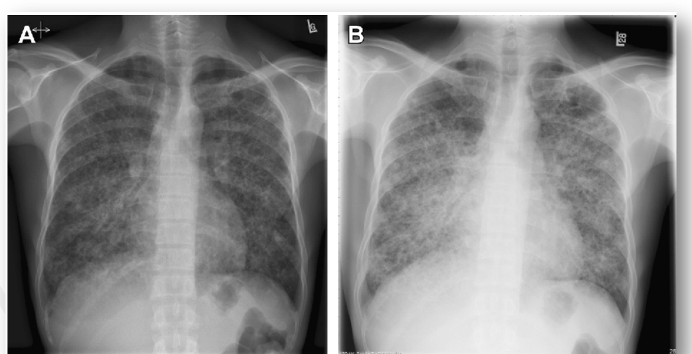
1. Co-infections
2. Resistance
3. Clinical failure

**Clinical failure** is the lack of improvement or worsening of respiratory function documented by arterial blood gases after ≥4 days to 8 days of anti-PcP treatment

- Persistent **fever**, **worsening hypoxia**, and/or **radiographic deterioration**

Failure attributed to:

- Lack of drug efficacy **(~7-10%)** in patients with mild-to-moderate PcP disease
- Treatment-limiting toxicities **(~33%)**

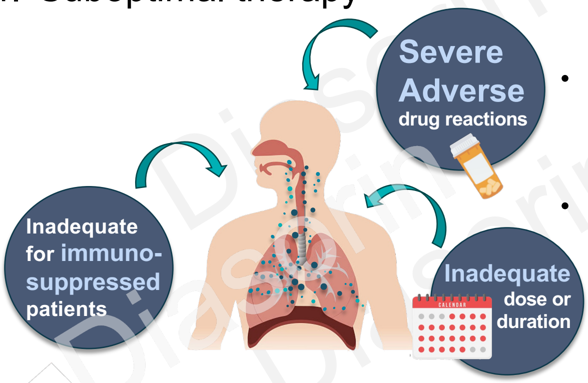



(A) Chest radiograph on admission with PcP. (B) Chest radiograph [same patient as (A)], after an interval of 3 days, showing marked deterioration in radiographic abnormalities.


- https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/pneumocystis-0
- Benfield, Thomas MD, DMSci*; Atzori, Chiara MD†; Miller, Robert F MB BS, FRCP‡; Helweg-Larsen, Jannik MD, DMSci§. Second-Line Salvage Treatment of AIDS-Associated Pneumocystis jirovecii Pneumonia: A Case Series and Systematic Review. JAIDS Journal of Acquired Immune Deficiency Syndromes 48(1):p 63-67, May 1, 2008.
- Miller, R.F., Huang, L., & Walzer, P.D. (2013). Pneumocystis pneumonia associated with human immunodeficiency virus. Clinics in chest medicine, 34 2, 229-41 .

# Treatment Prognosis Factors for *Pneumocystis* Pneumonia

1. Co-infections
2. Resistance
3. Clinical failure
4. Suboptimal therapy




**Challenge:** TMP-SMX must be administered in an appropriate way to achieve adequate antimicrobial activity while reducing concentration-dependent toxicities

- Toxicity
  - TMP-SMX is associated with **severe adverse** events in up to 57% of HIV-infected patients
- Drug-drug interactions
  - **TMP-SMX doesn't play nice with other medications**
    - Limits the use in patients with underlying hematologic diagnoses or solid organ transplants (~75% of PcP cases)
- Dose optimization
  - Inadequate dose escalation and duration
    - Limited studies are available to improve dosing strategies to prevent initial occurrence or recurrence of PcP

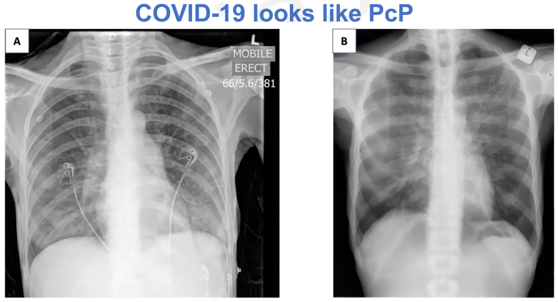

- https://www.idsociety.org/practice-guideline/prevention-and-treatment-of-opportunistic-infections-among-adults-and-adolescents/
- https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/whats-new
- Butler-Laporte G, Smyth E, Amar-Zifkin A, Cheng MP, McDonald EG, Lee TC. Low-Dose TMP-SMX in the Treatment of Pneumocystis jirovecii Pneumonia: A Systematic Review and Meta-analysis. Open Forum Infect Dis. 2020 Apr 2;7(5):ofaa112. doi: 10.1093/ofid/ofaa112. PMID: 32391402; PMCID: PMC7200085.




# Treatment Prognosis Factors for *Pneumocystis* Pneumonia

1. Co-infections
2. Resistance
3. Clinical failure
4. Suboptimal therapy
5. Incorrect diagnosis

**COVID-19 looks like PcP**




**PcP can be difficult to diagnose due to the following:**

- Non-specific clinical features
- Missed diagnosis due to high burden of opportunistic infections
- Failure in detection
  - The organism cannot be cultured
  - Invasive procedures (e.g., BALs, lung biopsies)
  - Unreliable diagnostic tests (low fungal burden or accuracy depends on highly skilled operators)


- https://www.idsociety.org/practice-guideline/prevention-and-treatment-of-opportunistic-infections-among-adults-and-adolescents/
- https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/whats-new
- Bateman, M., Oladele, R., & Kolls, J. K. (2020). Diagnosing Pneumocystis jirovecii pneumonia: A review of current methods and novel approaches. Medical mycology, 58(8), 1015–1028. https://doi.org/10.1093/mmy/myaa024
- Arshad V, Iqbal N, Saleem HA, Irfan M. Case of undiagnosed pneumocystis pneumonia (PCP). BMJ Case Rep. 2017 Oct 24;2017:bcr2017221871. doi: 10.1136/bcr-2017-221871. PMID: 29066657; PMCID: PMC5665312.
- Kelly S, Waters L, Cevik M, Collins S, Lewis J, Wu MS, Blanchard TJ, Geretti AM. Pneumocystis pneumonia, a COVID-19 mimic, reminds us of the importance of HIV testing in COVID-19. Clin Med (Lond). 2020 Nov;20(6):590-592. doi: 10.7861/clinmed.2020-0565. PMID: 33199326; PMCID: PMC7687333.

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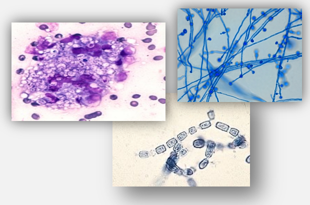
# Blastomycosis, Coccidioidomycosis, and Histoplasmosis

## The Deadly Shapeshifters Dimorphic Fungi



# Endemic and Dimorphic Mycoses in the Americas


- Thermally dimorphic endemic fungi have a **limited geographic range** and can cause both **primary disease and opportunistic infections.**

**The Americas contain the largest number of dimorphic endemic fungal species, including:**

| *Coccidioides* species | *Histoplasma capsulatum* | *Blastomyces* species | *Paracoccidioides* species | *Sporothrix* species |
|---|---|---|---|---|

- The fungal group affects different populations, including **immunocompetent individuals** exerting a substantial medical burden.
- Associated with outbreaks due to common environmental exposure.

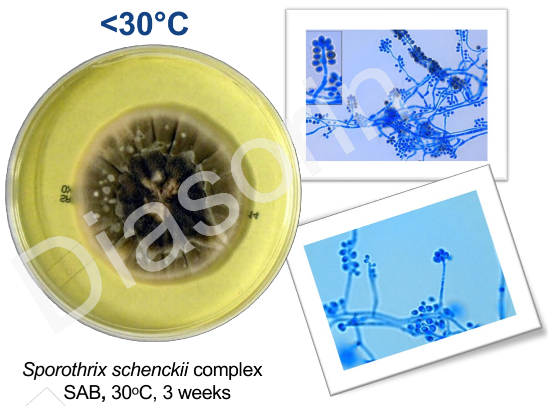
The picture can't be displayed.


- https://www.cdc.gov/fungal/diseases/
- Lockhart SR, Toda M, Benedict K, Caceres DH, Litvintseva AP. Endemic and Other Dimorphic Mycoses in The Americas. J Fungi (Basel). 2021 Feb 20;7(2):151. doi: 10.3390/jof7020151. PMID: 33672469; PMCID: PMC7923431.

# Thermal Dimorphism as a Fungal Pathogenic Trait

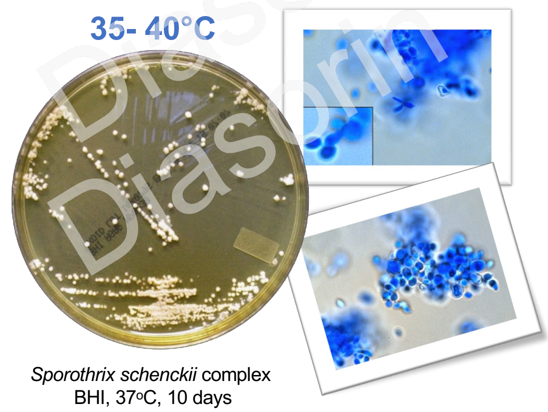
| Environmental Form | Pathogenic Form |
|---|---|
| Mycelial phase, sporulation reproduction | Yeast phase, budding, or endospores reproduction |

**<30°C**



*Sporothrix schenckii* complex
SAB, 30°C, 3 weeks

**35- 40°C**



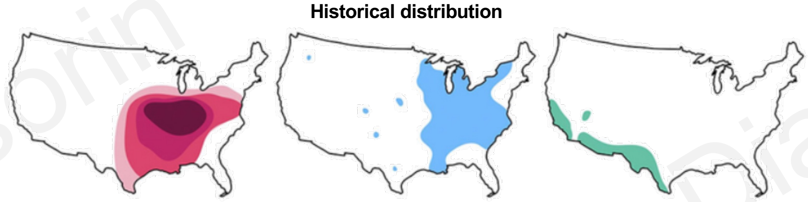
*Sporothrix schenckii* complex
BHI, 37°C, 10 days


• Yuri (2015, May 10). Fun With Microbiology (What's Buggin' You?): Sporothrix schenckii Complex. https://thunderhouse4-yuri.blogspot.com/2015/05/sporothrix-schenckii-complex-revisited.html

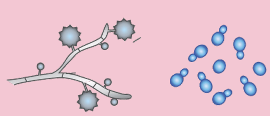



# Systemic Endemic Mycoses

**Historical distribution**

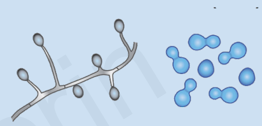


### Histoplasmosis: Ohio Valley Fever



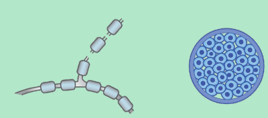
- Distributed worldwide, most prevalent in eastern and central regions of US
- Atypical pneumonia infection
- May disseminate to liver, spleen, and lungs

### Blastomycosis



•Distributed in the soil of a large section of the midwestern and southeastern US
•Atypical pneumonia
•Chronic cutaneous, bone, and nervous system complications

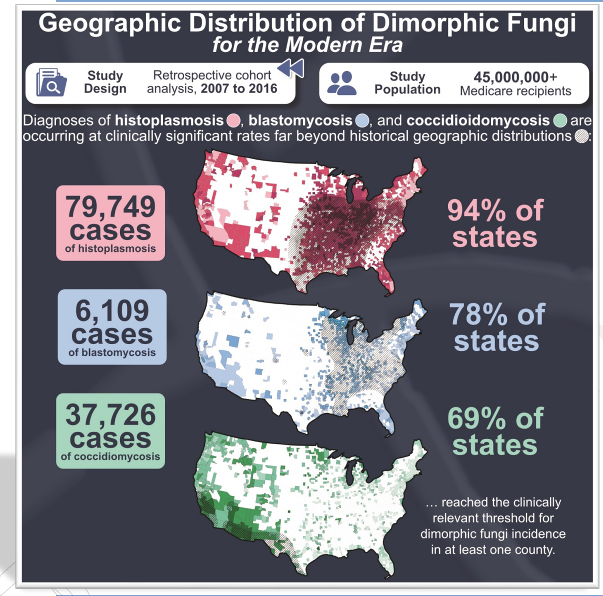
### Coccidioidomycosis: Valley Fever



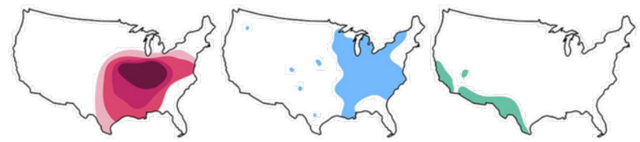
• Distributed worldwide, most prevalent in California, southwestern US, Puerto Rico
•Atypical pneumonia
•May disseminate to skin, joints, bones, and meninges


• Sil A, Andrianopoulos A. Thermally Dimorphic Human Fungal Pathogens--Polyphyletic Pathogens with a Convergent Pathogenicity Trait. Cold Spring Harb Perspect Med. 2014;5(8):a019794. Published 2014 Nov 10. doi:10.1101/cshperspect.a019794
• https://www.cdc.gov/mmwr/volumes/71/ss/ss7107a1.htm

## The Geographic Distribution of Dimorphic Mycoses in the US is Expanding




**Historical distribution**



The dimorphic mycoses are being diagnosed more frequently in areas where they were not historically common

Geographic changes are likely multifactorial: **climate change** and **other anthropogenic activities**


- Clin Infect Dis, Volume 76, Issue 7, 1 April 2023, Pages 1295–1301, https://doi.org/10.1093/cid/ciac882
- Mazi PB, Sahrmann JM, Olsen MA, et al. The Geographic Distribution of Dimorphic Mycoses in the United States for the Modern Era. Clin Infect Dis. 2023;76(7):1295-1301. doi:10.1093/cid/ciac882




## Blastomycosis Incidence, Vermont, USA

Statewide annual incidence rates are **~0.2–2.0 cases**/100,000 persons

- Surveillance is limited to just five states: **Arkansas, Louisiana, Michigan, Minnesota**, and **Wisconsin**

They identified 114 patients (median age 55, 59% male) diagnosed with blastomycosis from 2011 through 2020

- Statewide incidence of blastomycosis was **1.8 cases**/100,000 persons

**Expanded surveillance is needed…**

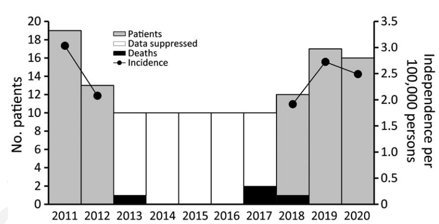



Figure 1. Numbers of patients with blastomycosis, attributable deaths per year, and annual incidence (cases/100,000 population) in Vermont, USA, 2011–2020.

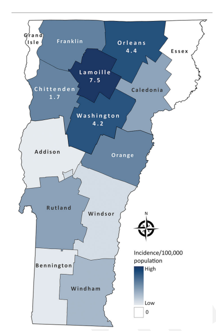



Figure 2. Geographic distribution of blastomycosis cases by county, Vermont, USA, 2011–2020. Numbers indicate incidence rates (cases/100,000 population) for counties with the highest incidence.


- Borah BF, Meddaugh P, Fialkowski V, et al. Using Insurance Claims Data to Estimate Blastomycosis Incidence, Vermont, USA, 2011–2020. Emerging Infectious Diseases. 2024;30(2):372-375. doi:10.3201/eid3002.230825.

# The Growing Challenges of Fungal Infections

## Diagnosis

- Clinical awareness
- Standardized guidelines for the diagnosis and treatment
- Delays or lack of access to healthcare

- New diagnostic tools
- Better training for clinicians
- Focus on neglected populations

## Limited Treatments

- Cytotoxicity or side effects
- Interactions with other drugs
- Lack of access in developing countries

- Development of novel therapeutic alternatives
- Focus on neglected populations

## Emerging Pathogens

- Climate change
- International trade
- Travel

- Education and awareness
- Expanding clinical screening and surveillance
- Environmental sampling

## Resistance

- Overuse of antibiotics
- Agrochemicals and antifungals in crop cultivation

- Antimicrobial stewardship
- Mycoparasitism-based strategies in agriculture

## Fungal Burden

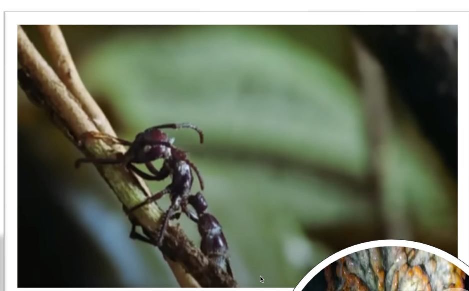
- Infections are rarely communicable
- Lack of public health interest
- Lack of incidence and prevalence

- Surveillance
- Global research in public health, food biosecurity, and biodiversity


- Rodrigues ML, Nosanchuk JD. Fungal diseases as neglected pathogens: a wake-up call to public health officials. PLoS Negl Trop Dis 2020; 14:e0007964.
- Formanek PE, Dilling DF. Advances in the diagnosis and management of invasive fungal disease. Chest 2019; 156:834–42.
- Almeida F, Rodrigues ML, Coelho C. The Still Underestimated Problem of Fungal Diseases Worldwide. Front Microbiol. 2019 Feb 12;10:214. doi: 10.3389/fmicb.2019.00214. PMID: 30809213; PMCID: PMC6379264.
- Nnadi NE, Carter DA. Climate change and the emergence of fungal pathogens. PLoS Pathog. 2021 Apr 29;17(4):e1009503. doi: 10.1371/journal.ppat.1009503. PMID: 33914854; PMCID: PMC8084208.




# Could Fungi be the Next Pandemic Threat?



Cordyceps BBC; The Last of Us (HBO)

The show may not depict reality accurately. In truth, reality can be more terrifying…

- Fungi are relatively slow mutators,
  *however, the cases of drug-resistant fungal infections are increasing rapidly*
- Healthy immune systems,
  *however, the advances in modern medicine have made millions of people newly susceptible to fungal infections*
- Human body temperature,
  *however, shifting temperatures caused by climate change can alter fungi's genetics, impacting their survival at higher temperatures and potentially aiding human adaptation (Gusa, Asiya et al. 2023)*
- Infections are rarely communicable,
  *however, many fungi are mobile and dispersed by airborne spores*
- No fungus turns ordinary people into zombies,
  *however, our minds can definitely be altered by a fungus (e.g., psilocybin, aka "magic mushrooms," ergot)*
- No fungi have caused a deadly pandemic in people,
  *however, they have caused devastating outbreaks in wildlife and our global food supply*


- Cordyceps: attack of the killer fungi - Planet Earth Attenborough BBC wildlife https://www.youtube.com/watch?v=XuKjBIBBAL8

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