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WÜRZBURG

NRZMyk

Not all fungi are the same

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Leibniz Institute for Natural Product Research and Infection Biology – HKI, Jena

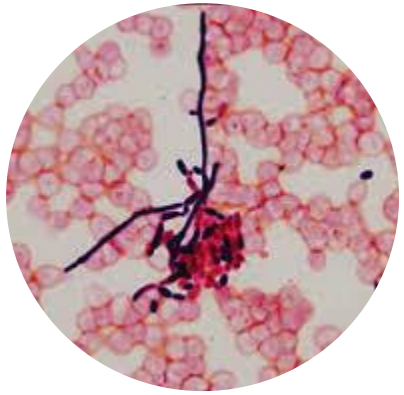
HDM-FUN

@okurzai

Leibniz-Gemeinschaft

HKI

Candidemia yesterday…

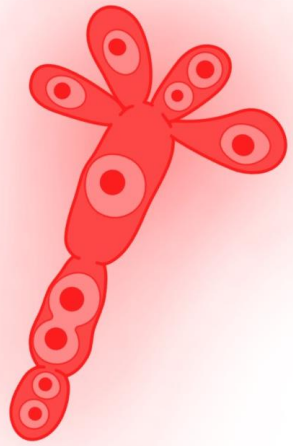


> 50% *Candida albicans*

- well known optimum treatment
- established source management
- hardly any resistance
- no IPC measures

Issues for Clinical Management

- Novel & emerging pathogens
- Aquired drug resistance
- Hospital transmission

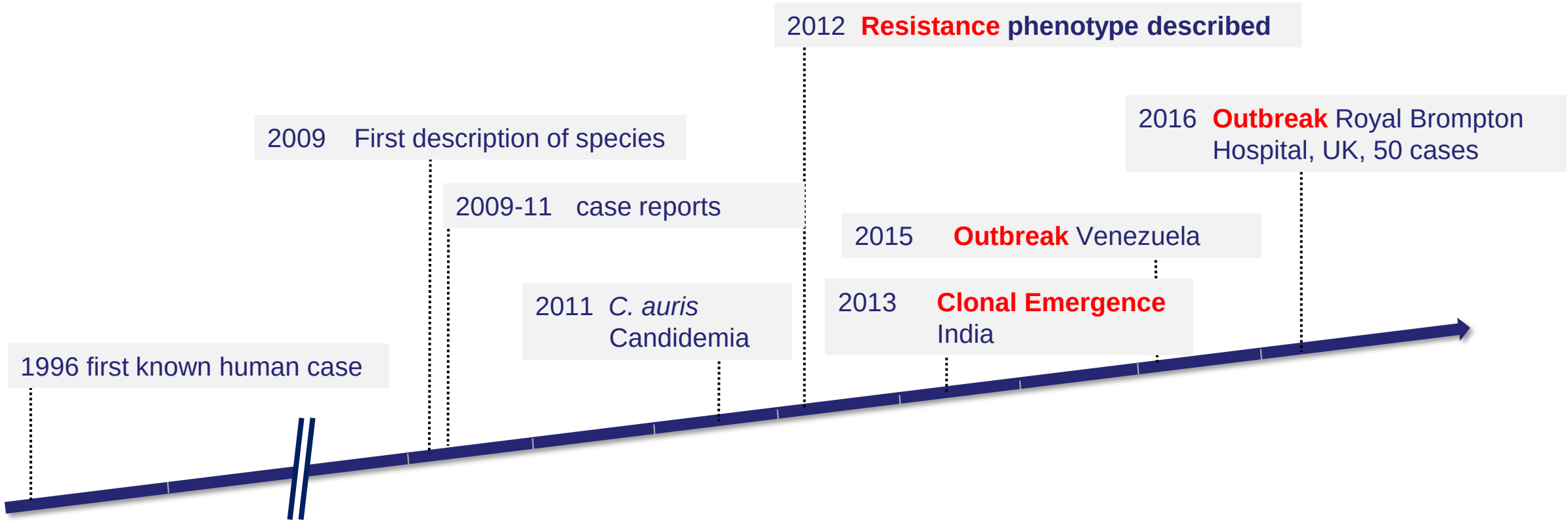


Fungal „Superbug“

WHO fungal priority pathogens list to guide research, development and public health action

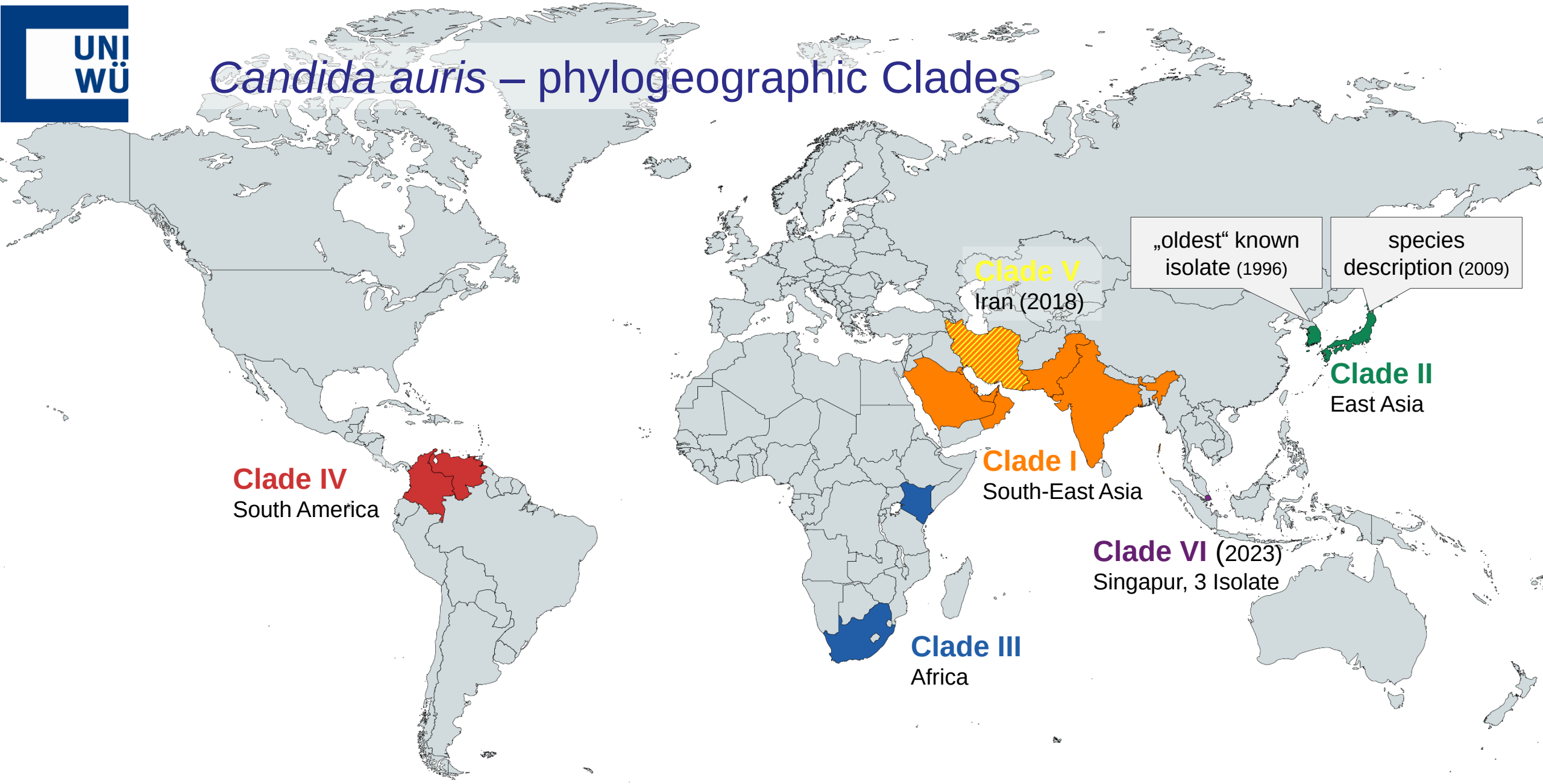
World Health Organization

Candida auris



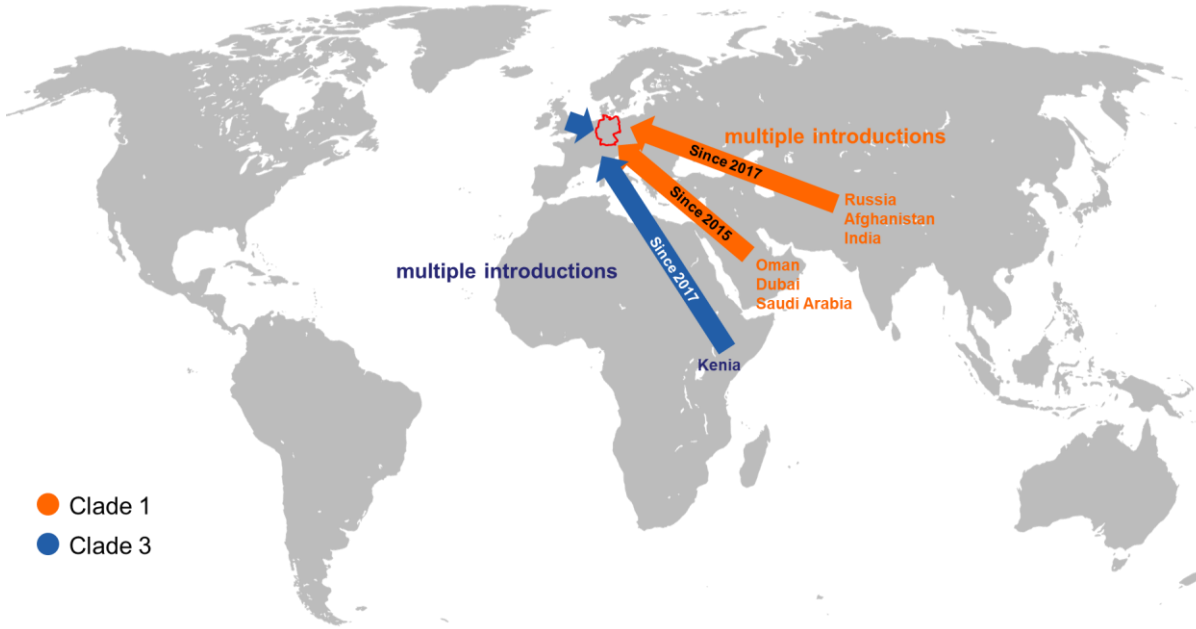
Antifungal Drug Resistance & Patient to Patient Transmission

Candida auris – phylogeographic Clades



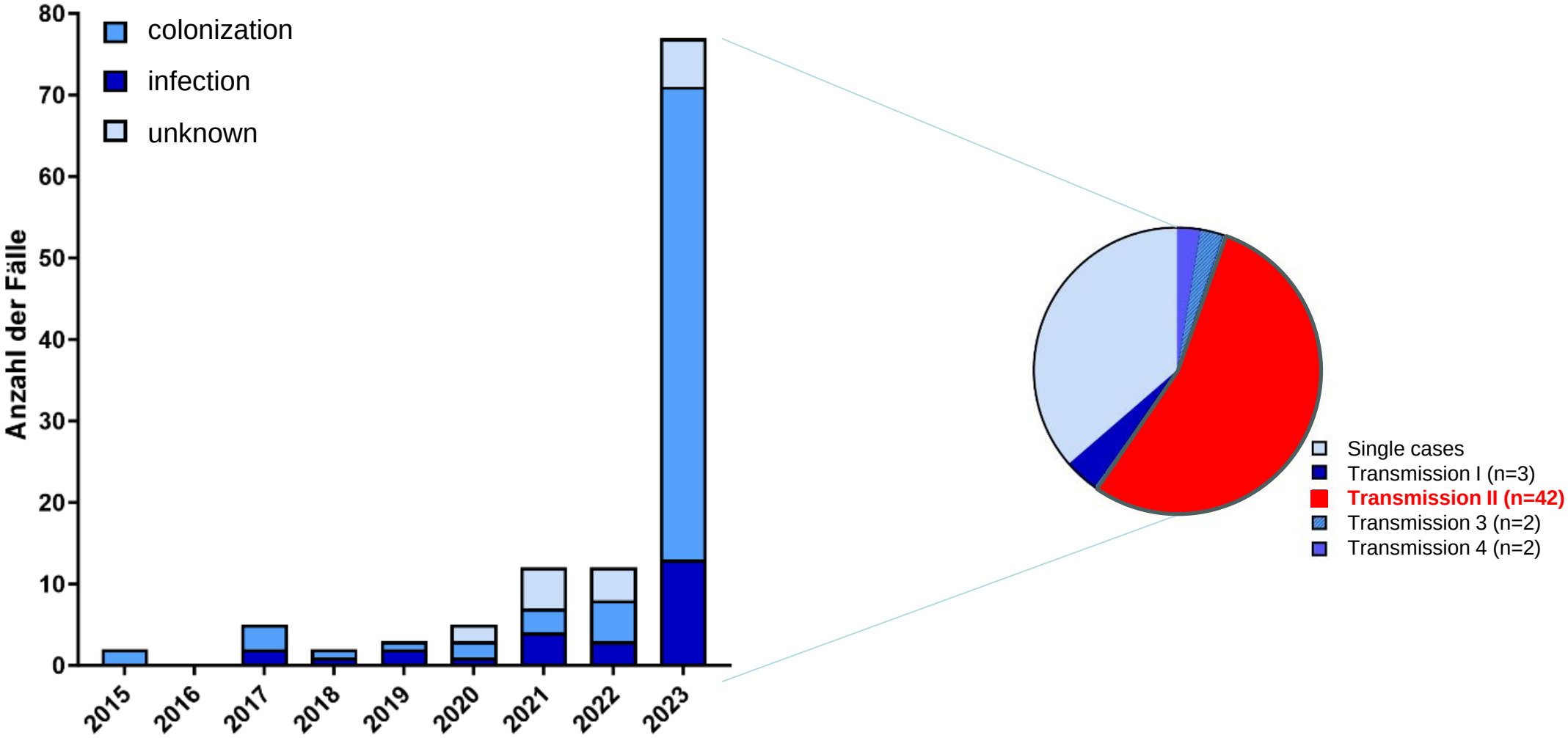
C. auris in D – Invasion into Germany

2015	First kown case in D
2016-20	<10 cases per yr, often „medical imports“
2021	First documented transmission
2022	**National IPC Recommendations** published
2023	**Mandatory reporting** for *C. auris* detection in primary sterile samples (§7IfSG)



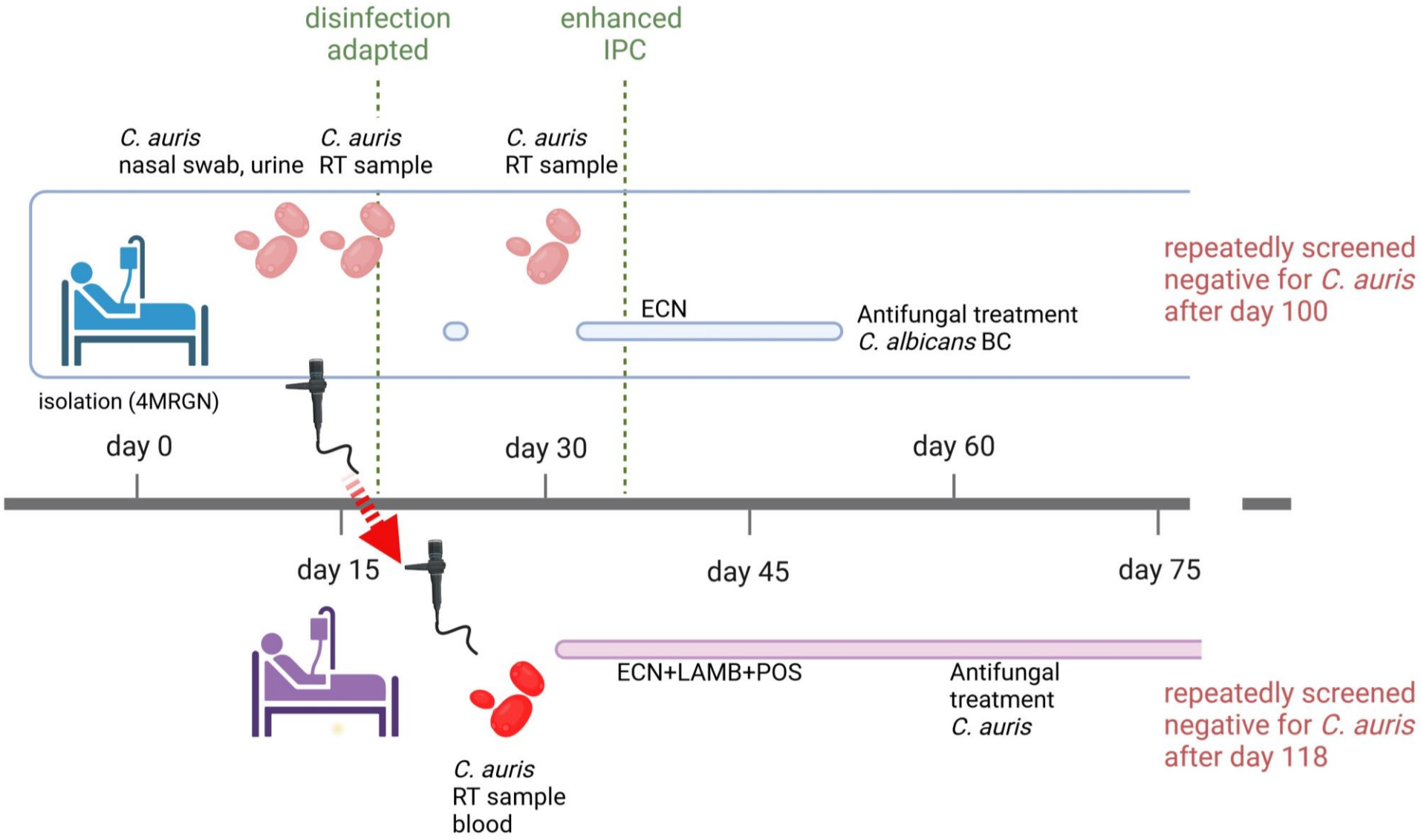
Hamprecht *et al.,* Emerging Infect Dis, 2019
Aldejohann *et al.,* Dtsch Arztebl Int. 2023

Candida auris in Germany, current situation



Aldejohann *et al.*, Epi Bull 2024

Candida auris Transmission event @Charité 2021



Wiese-Posselt, Hinrichs *et al.*, Mycoses 2022

Candida auris transmission

Wiese-Posselt, Hinrichs *et al.,* Mycoses 2022

Candida auris transmission

Wiese-Posselt, Hinrichs *et al.,* Mycoses 2022

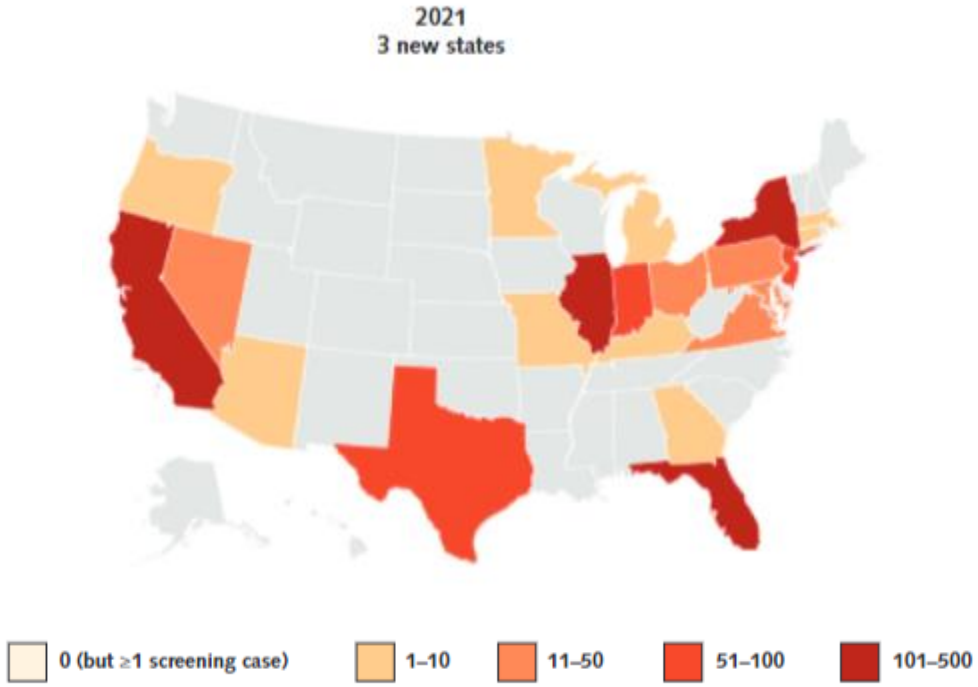
Eyre *et al.,* New Engl J Med 2018

Nobrega de Almeida *et al.,* Mycoses 2021

(image not from publication - example only)

EU & US – aktuelle Situation

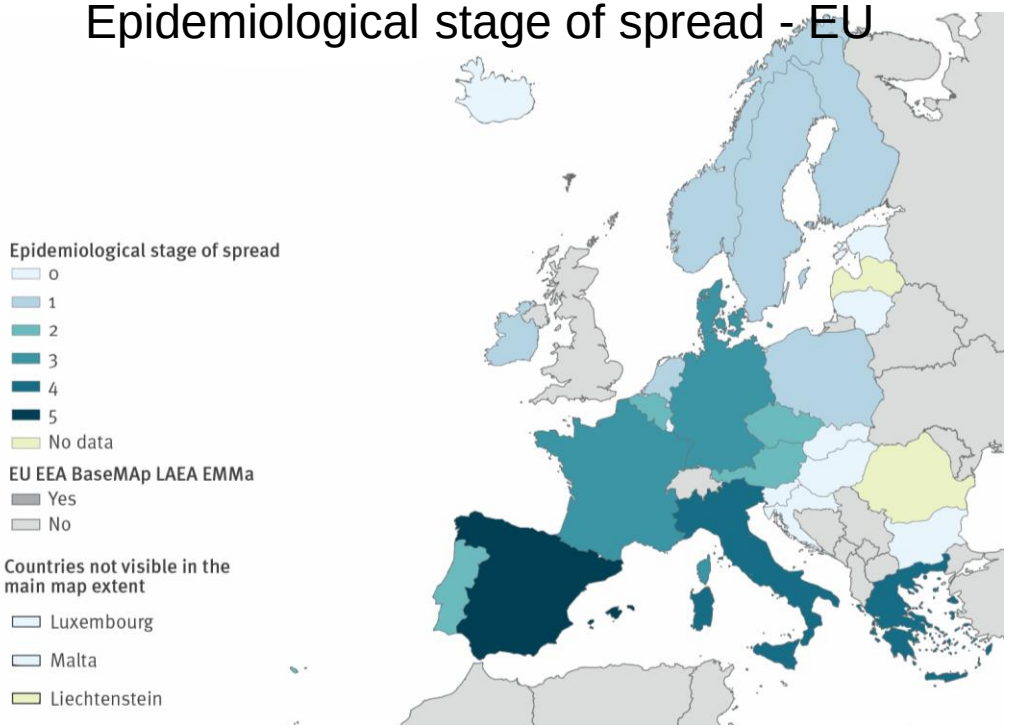
Clinical cases only - US



Worsening Spread of *C. auris* in the US, 2019 to 2021.
Lyman *et al.,* Ann Intern Med. 2023

Endemic in „some regions“

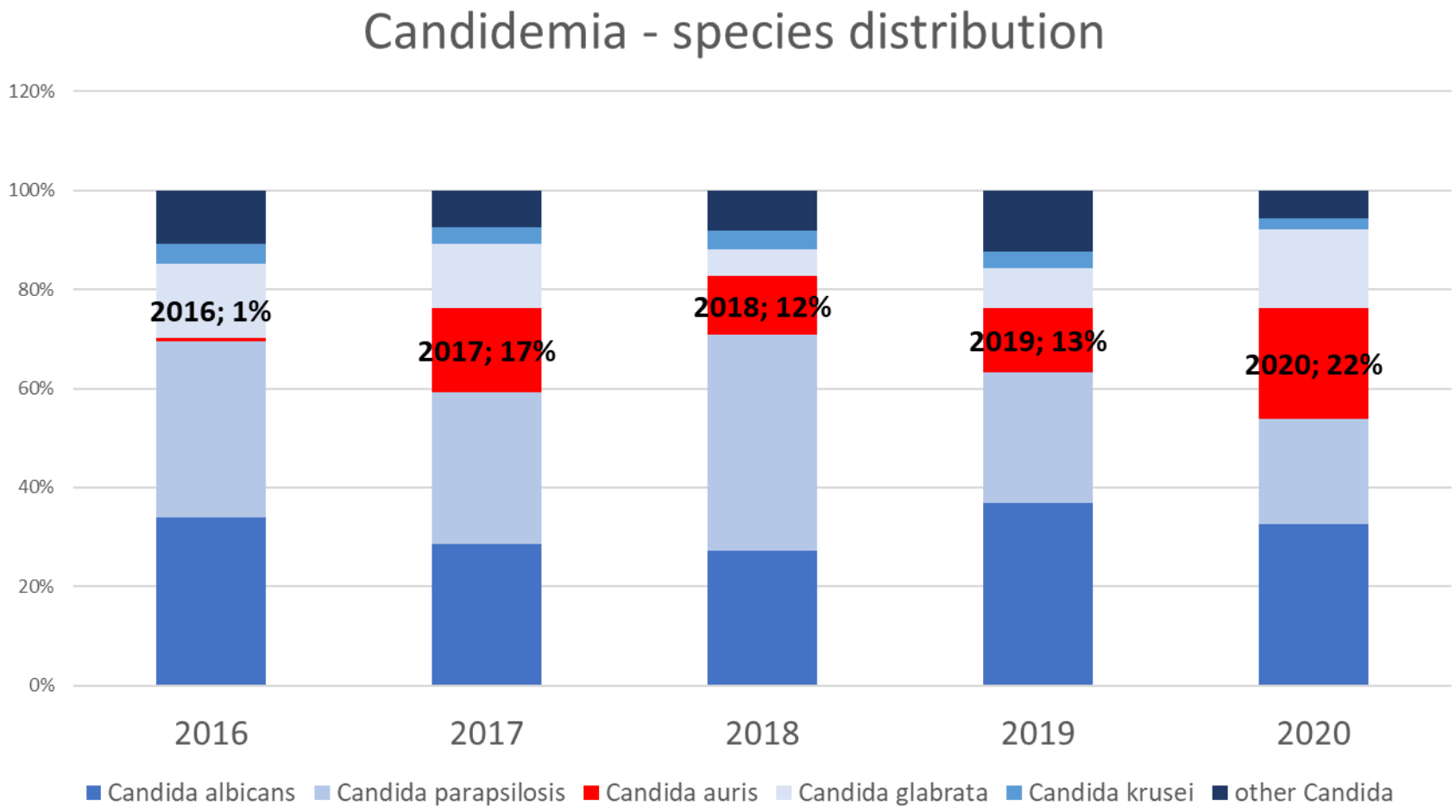
Epidemiological stage of spread - EU



Increasing number of cases and outbreaks caused by *C. auris* in the EU/EEA, 2020 to 2021.
Kohlenberg *et al.,* Euro Surveill. 2022

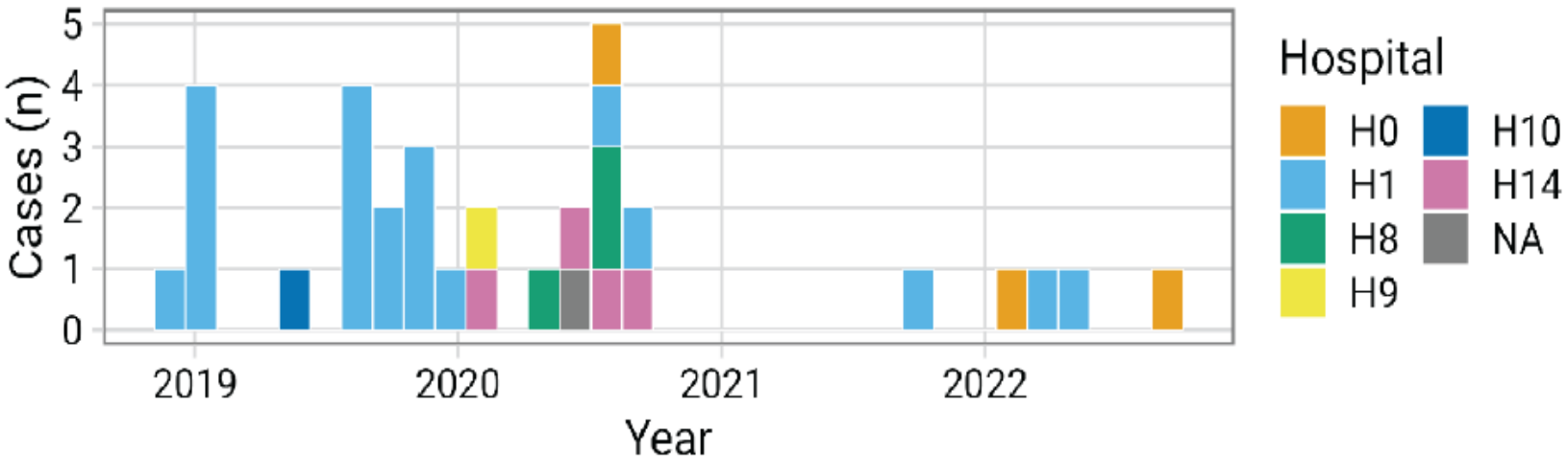
Endemic „in some regions in Spain“

Where will we go?



Chibabhai, S Afr J Infect Dis. 2022 (Johannesburg, tertiary care hospital)

What else? – Emerging resistant *Candida parapsilosis*



- Clonal Outbreak with FLU^{R} *C. parapsilosis*
- Several years, several hospitals

Abbildung: Brassington, Walther, Barber *https://www.medrxiv.org/content/10.1101/2024.02.22.24302918v1*

Candida parapsilosis - Outbreak

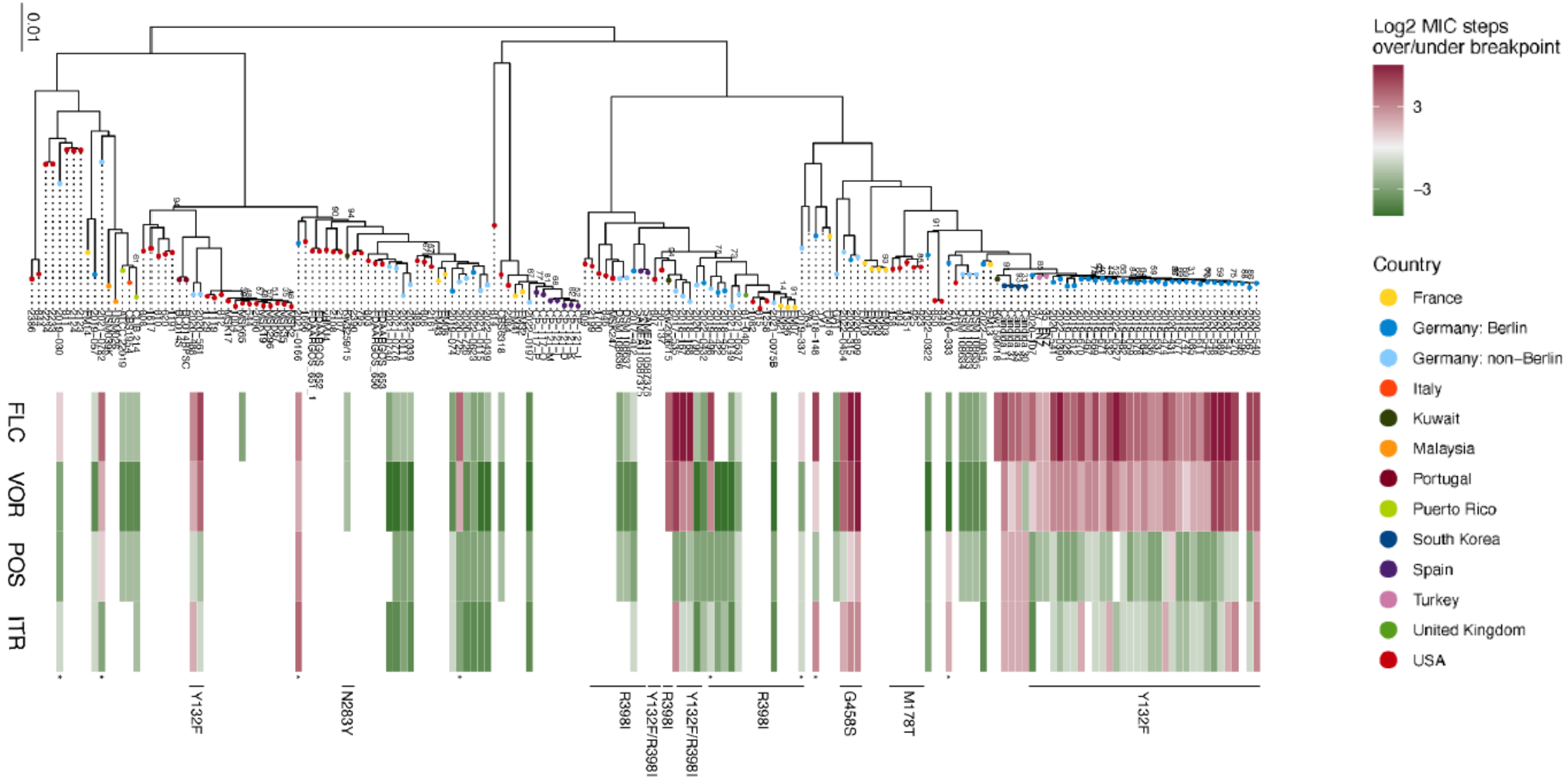


Abbildung: Brassington, Walther, Barber *https://www.medrxiv.org/content/10.1101/2024.02.22.24302918v1*

Fluconazole Resistance *versus* Transmissive Capacity?

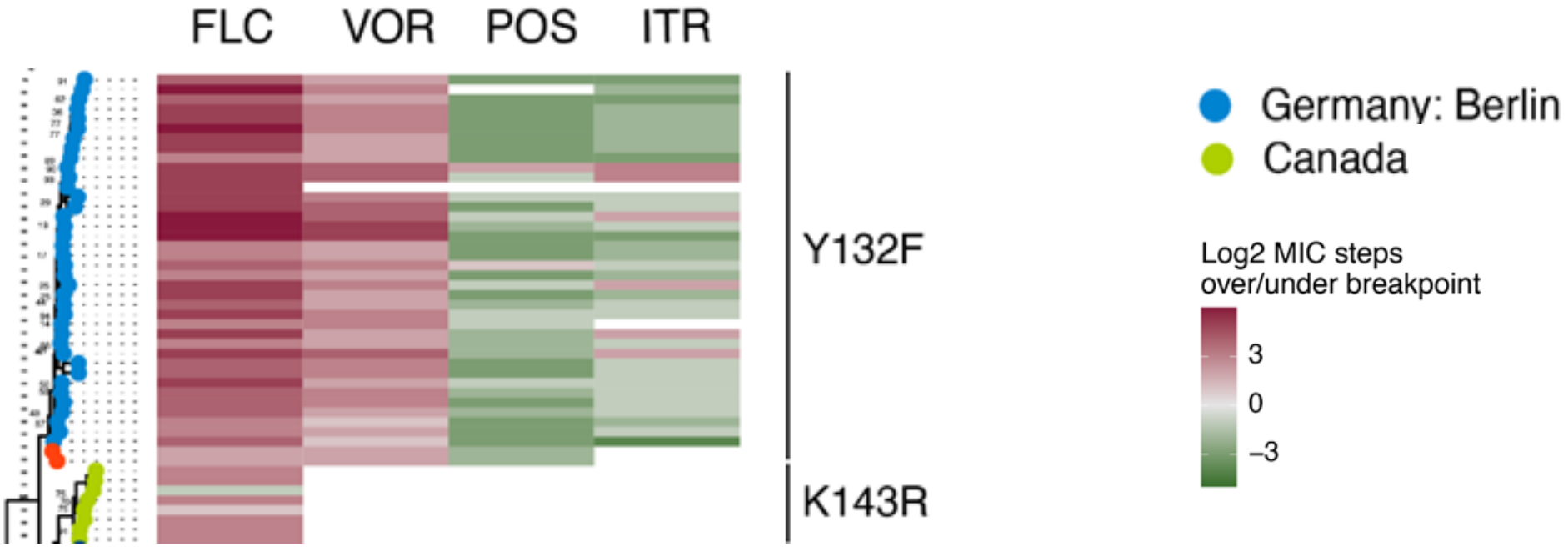


Abbildung: Brassington, Walther, Barber *https://www.medrxiv.org/content/10.1101/2024.02.22.24302918v1*

Aspergillosis yesterday…

Aspergillus fumigatus

- **Neutropenic patient:** invasive infection, that mostly is already treated
- **other patient:** contamination

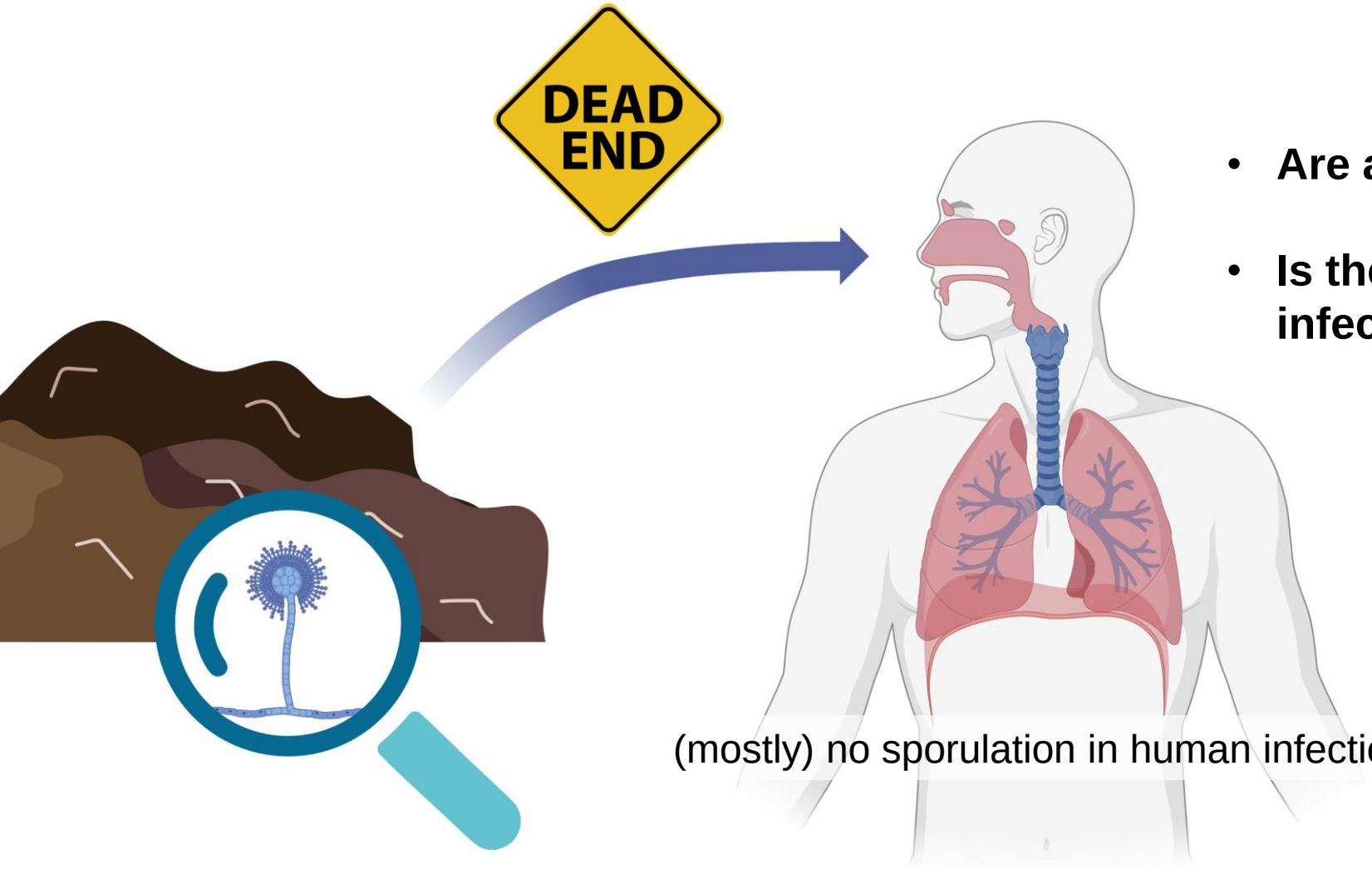
Aspergillosis today…

Aspergillus fumigatus

- **Neutropenic patient:** invasive infection, that mostly is already treated
- **other patient:** con[illegible]nination

  - IAPA
  - CAPA
  - chronic pulmonary aspergillosis
  - IA in COPD
  - IA in end-stage liver dysfunction

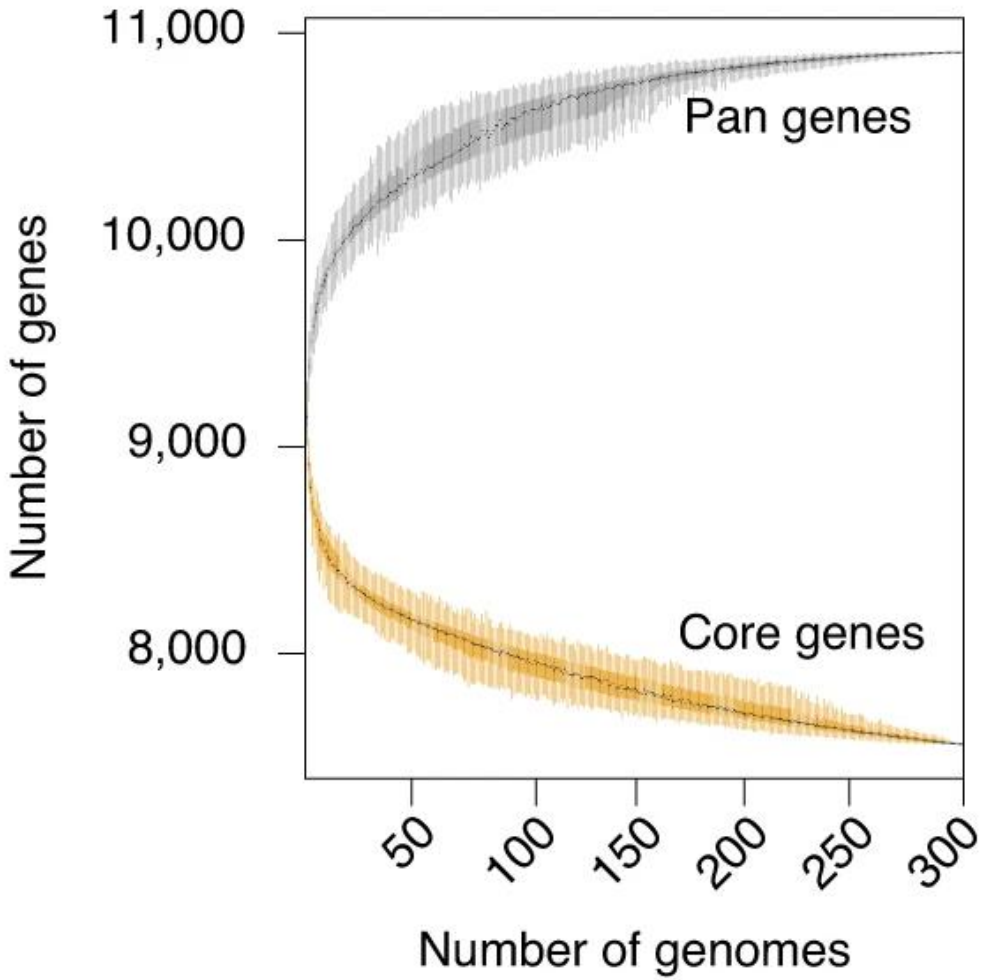
Aspergillus fumigatus

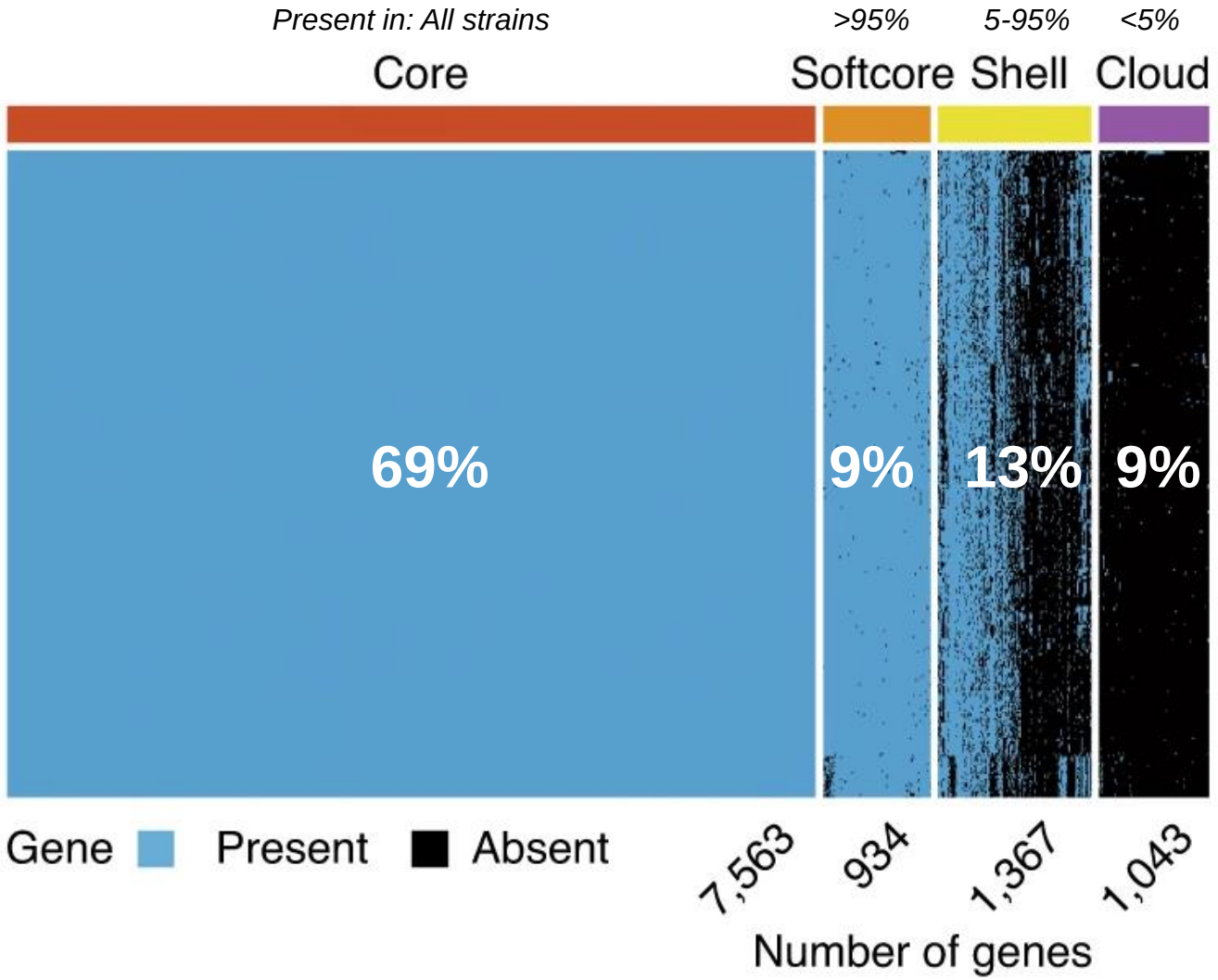


- **Are all *A. fumigatus* strains equal?**
- **Is there adaptation towards human infection?**

(mostly) no sporulation in human infections

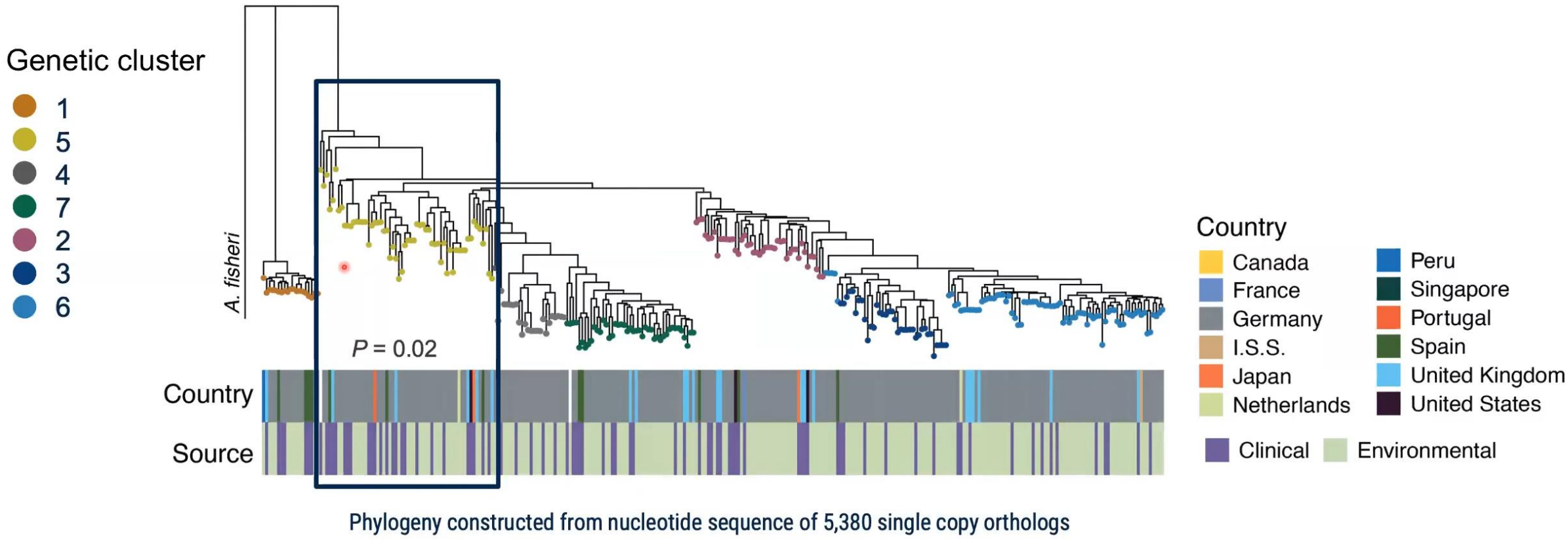
Pangenome Analysis *A. fumigatus*





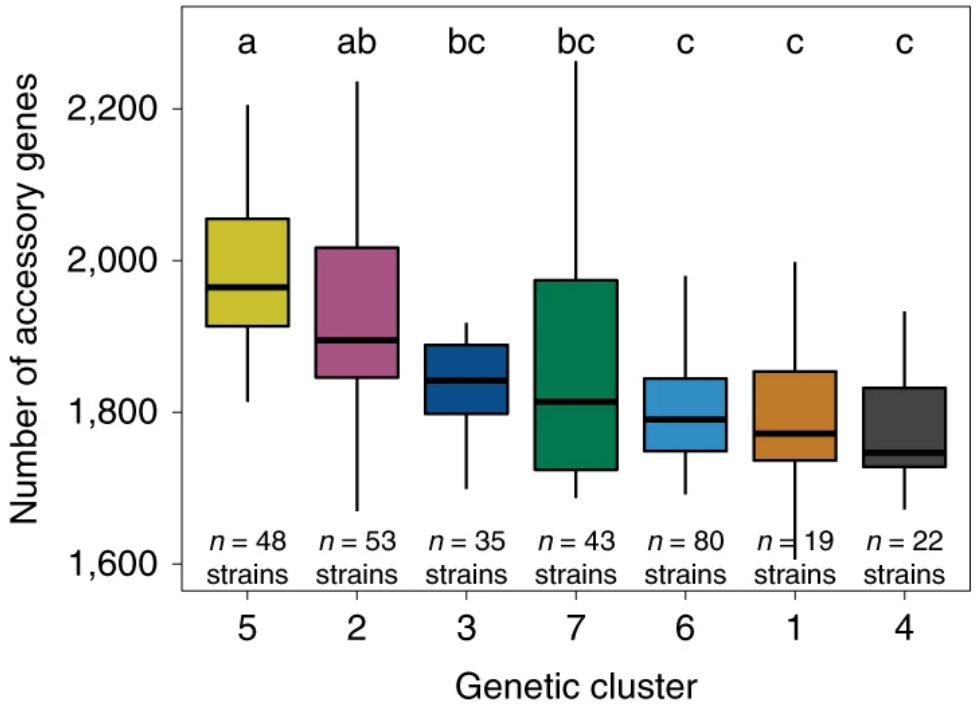
Barber *et al*. *Nat Microbiol* (2021)

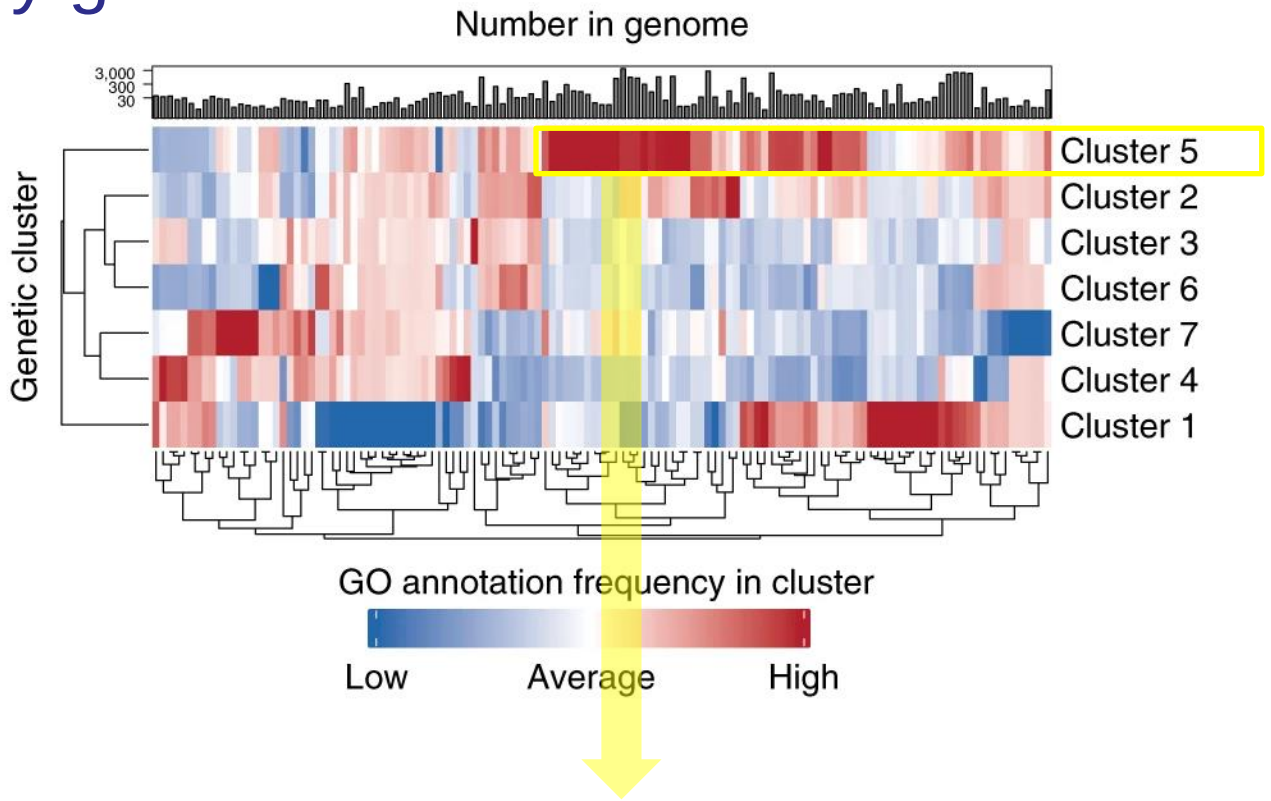
Enrichment for clinical isolates in genetic cluster 5



Barber *et al*. *Nat Microbiol* (2021)

Cluster 5 has more accessory genes



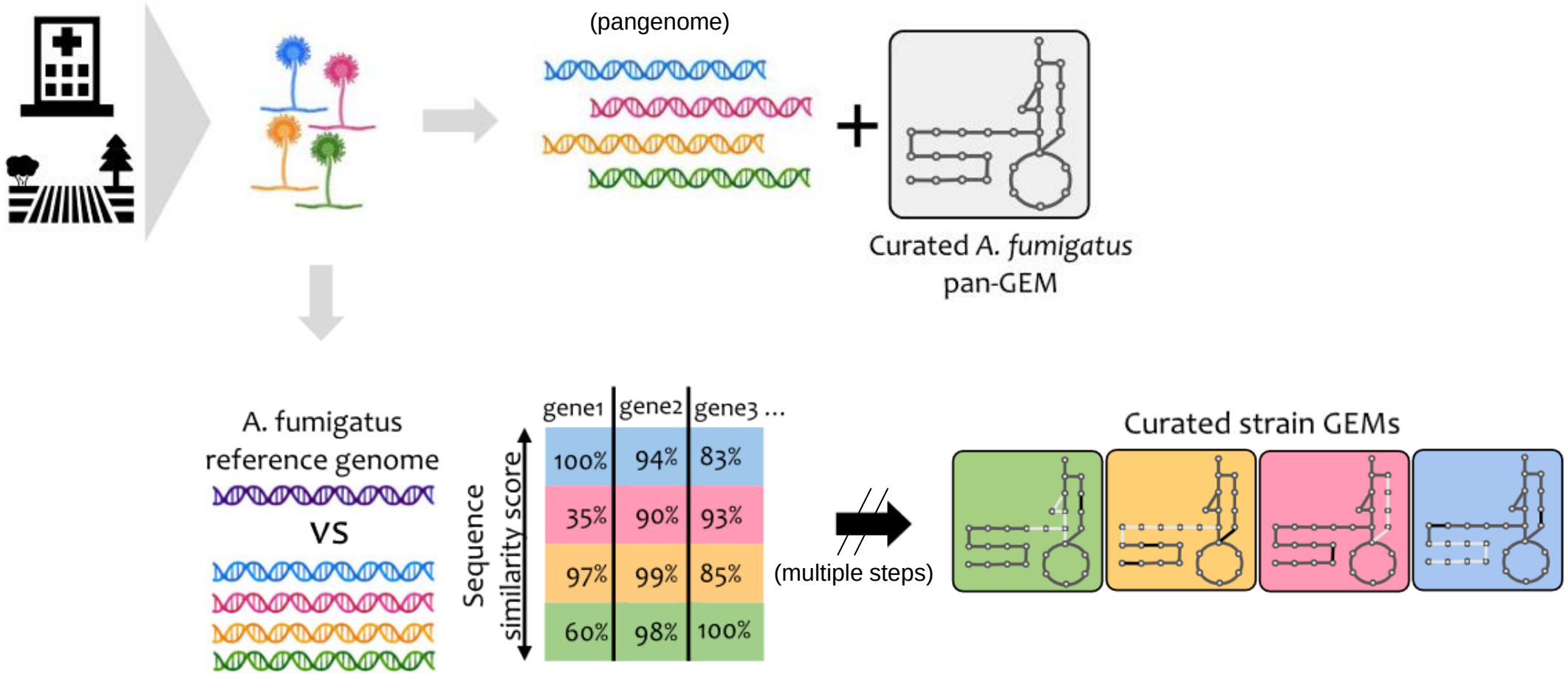


GO annotation

- Oxidation-reduction
- Transmembrane transporters
- Iron binding
- Carbohydrate Metabolism
- Proteolysis
- Nucleotide Binding

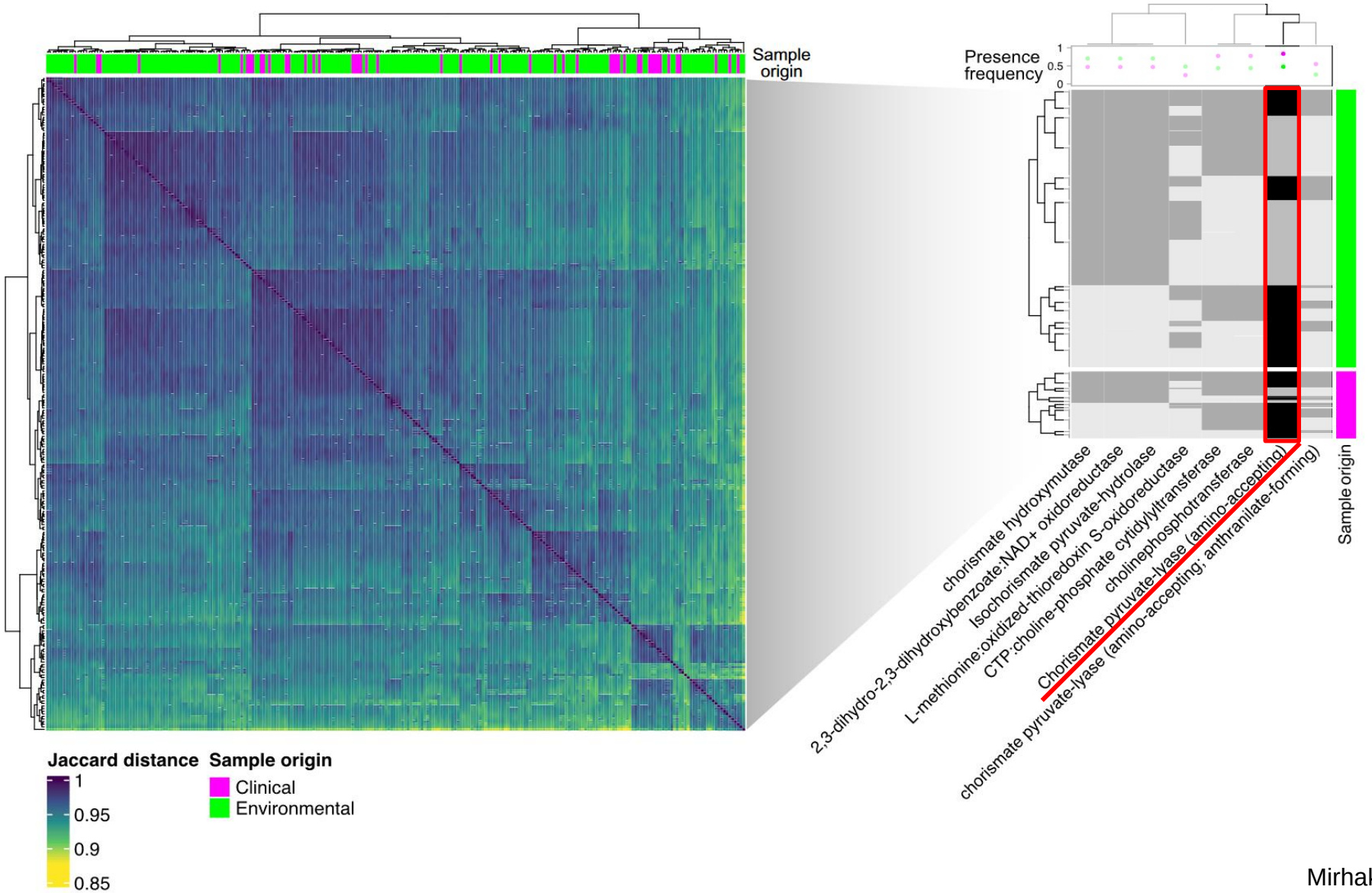
Barber *et al*. *Nat Microbiol* (2021)

Assigning functions to genes: Modeling metabolism of *A. fumigatus*



Mirhakkak *et al.,* Nature Comm. 2023

Metabolic differences clinical vs. environmental



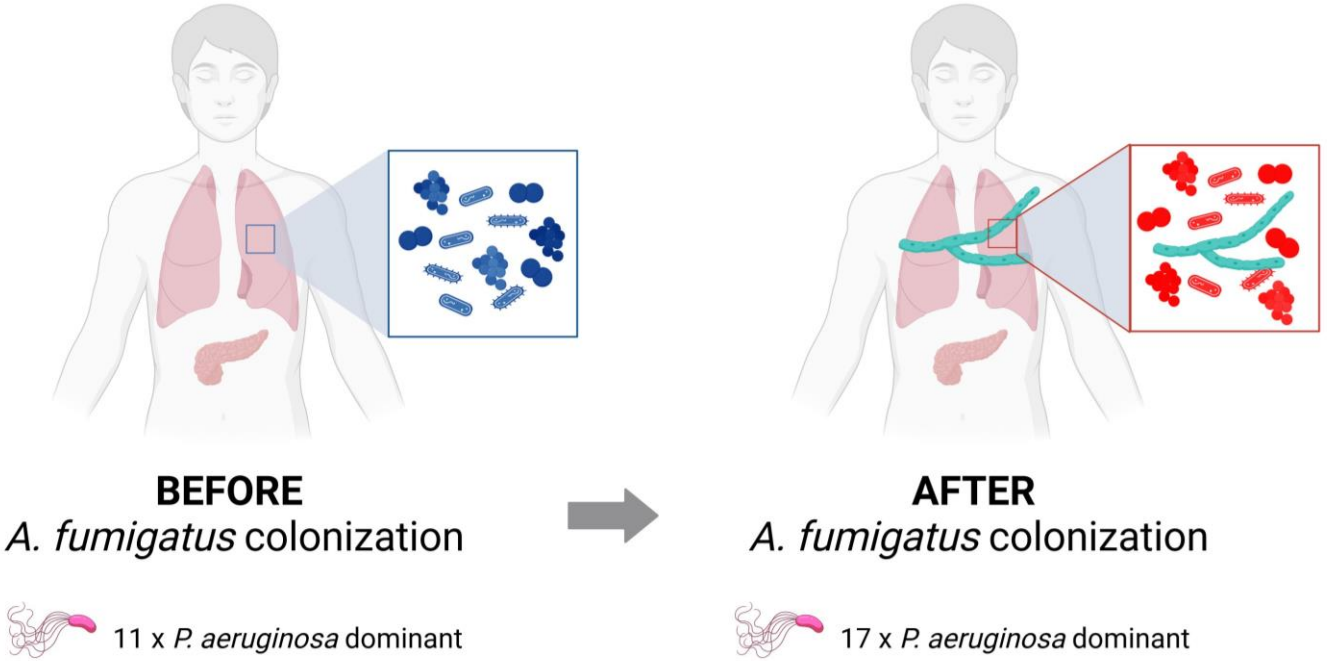
Mirhakkak *et al.,* Nature Comm. 2023

Metabolic differences clinical vs. environmental

- presence of chorismate lyase alone is a first predictor for “clinical”
- Chorismate lyase activity is linked to the shikimate pathway (biosynthesis of aromatic compounds), which has been associated with virulence in *A. fumigatus*.
- ability to add sulfur to methionine and absence of the ability to convert selenocystathione to selenocysteine or tryptamine to Indole-3-acetaldehyde is characteristic of environmental strains

Mirhakkak *et al.,* Nature Comm. 2023

Metabolic features in the host environment



Mirhakkak *et al.,* Nature Comm. 2023

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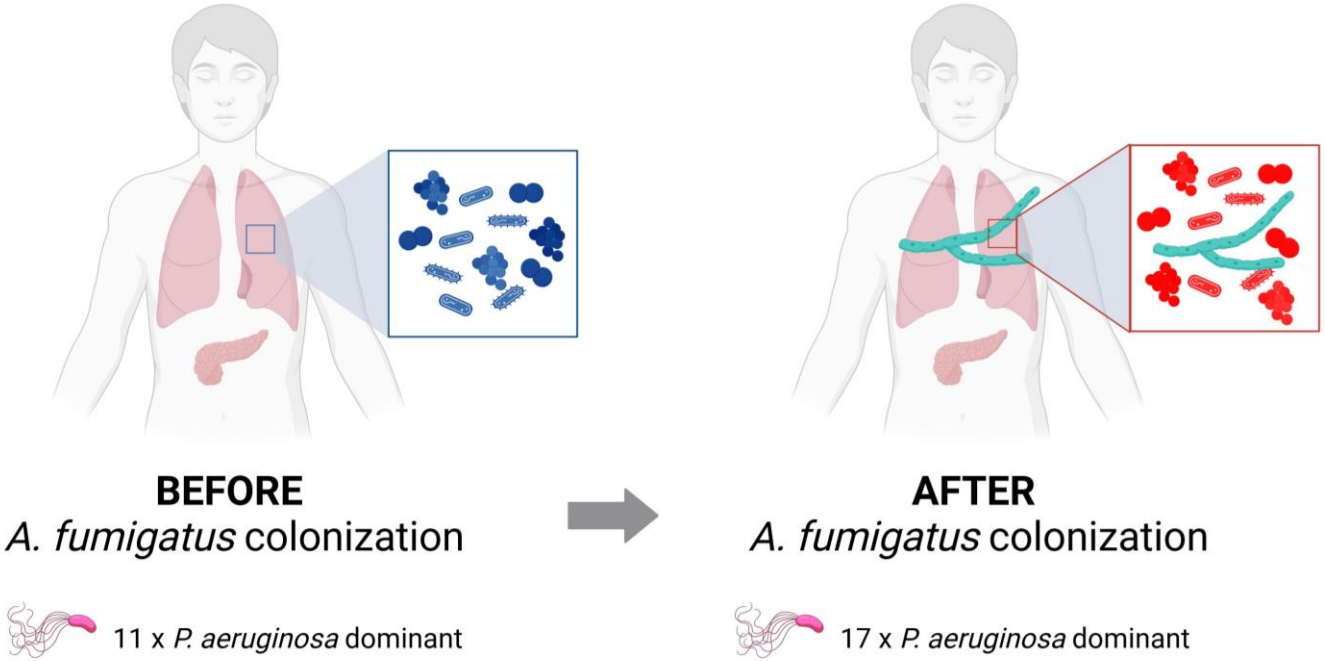
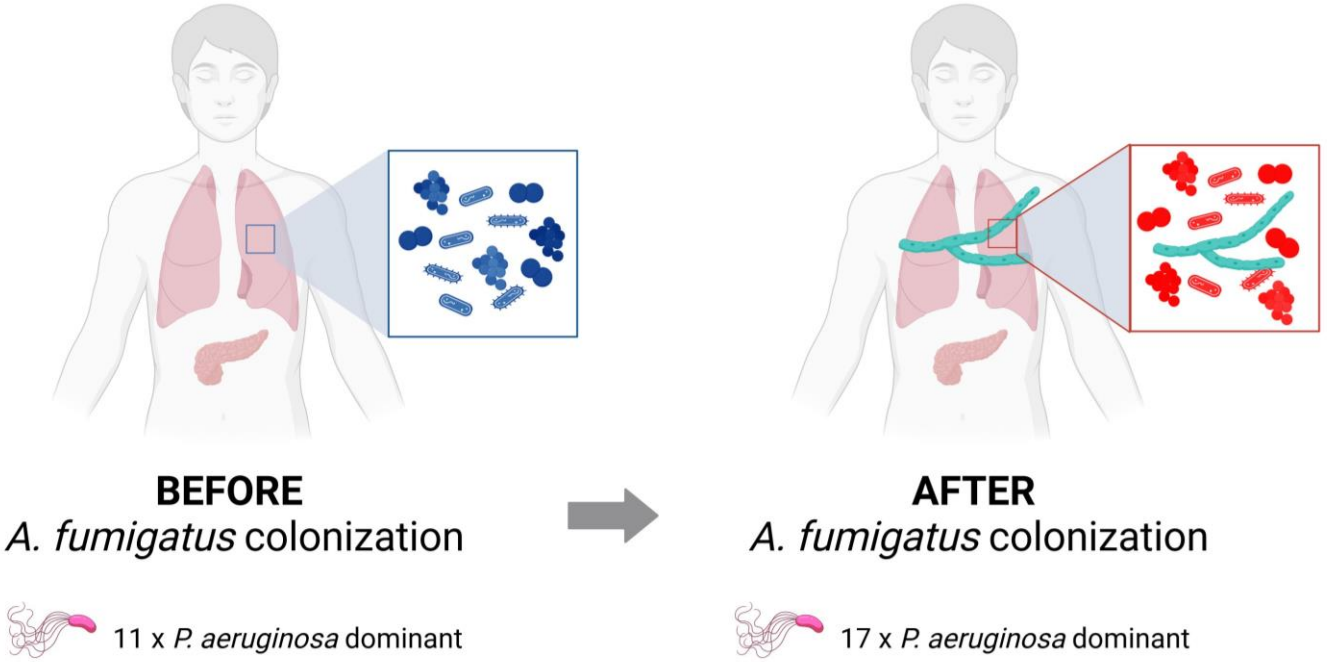


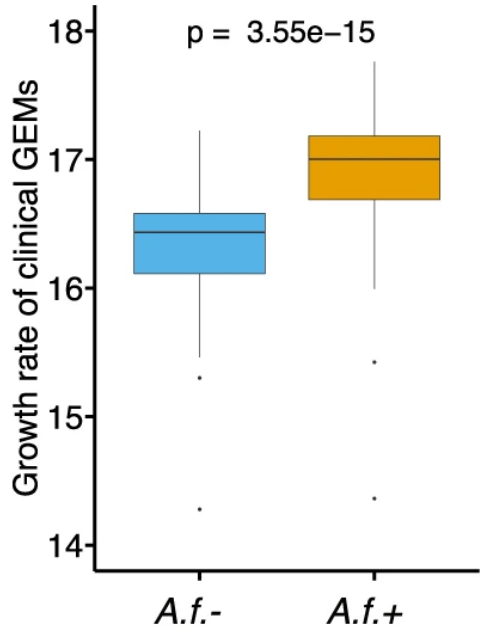
- Lung microbiome changes with *A. fumigatus* colonization
- Metabolic functions change particularly for aromatic amino acids
  (also fatty acid, nitrogen, sulfur metabolism)

Mirhakkak *et al.,* Nature Comm. 2023

Metabolic features in the host environment



- Lung microbiome changes with *A. fumigatus* colonization
- Metabolic functions change particularly for aromatic amino acids
  (also fatty acid, nitrogen, sulfur metabolism)
- These changes promote growth of *A. fumigatus*
  (clinical strain metabolic profile)

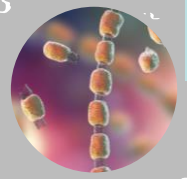


Mirhakkak *et al.,* Nature Comm. 2023

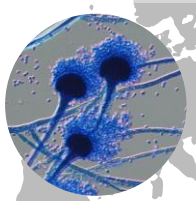
The world of fungal infections is changing

- Acquired resistance
- Newly emerging pathogens
- P2P transmission
- New patient cohorts affects
- Potential adaptation towards interaction with human host

Emergence of fungal infections since ~2000



Geographic expansion
Coccioides immitis



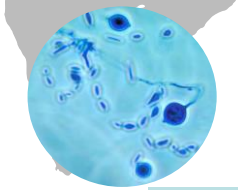
Azole resistance in Aspergillus
Aspergillus fumigatus

From banana to humans
Fusarium musae

Resistant dermatophytes
Trichophyton indotinae

Outbreak associated *Candida*
Candida auris
FLU^{R} Candida parapsilosis

Zoonotic sporothrichosis
Sporothrix brasiliensis



New fungal threats in Africa
Emergomyces spp.
Histoplasma spp.

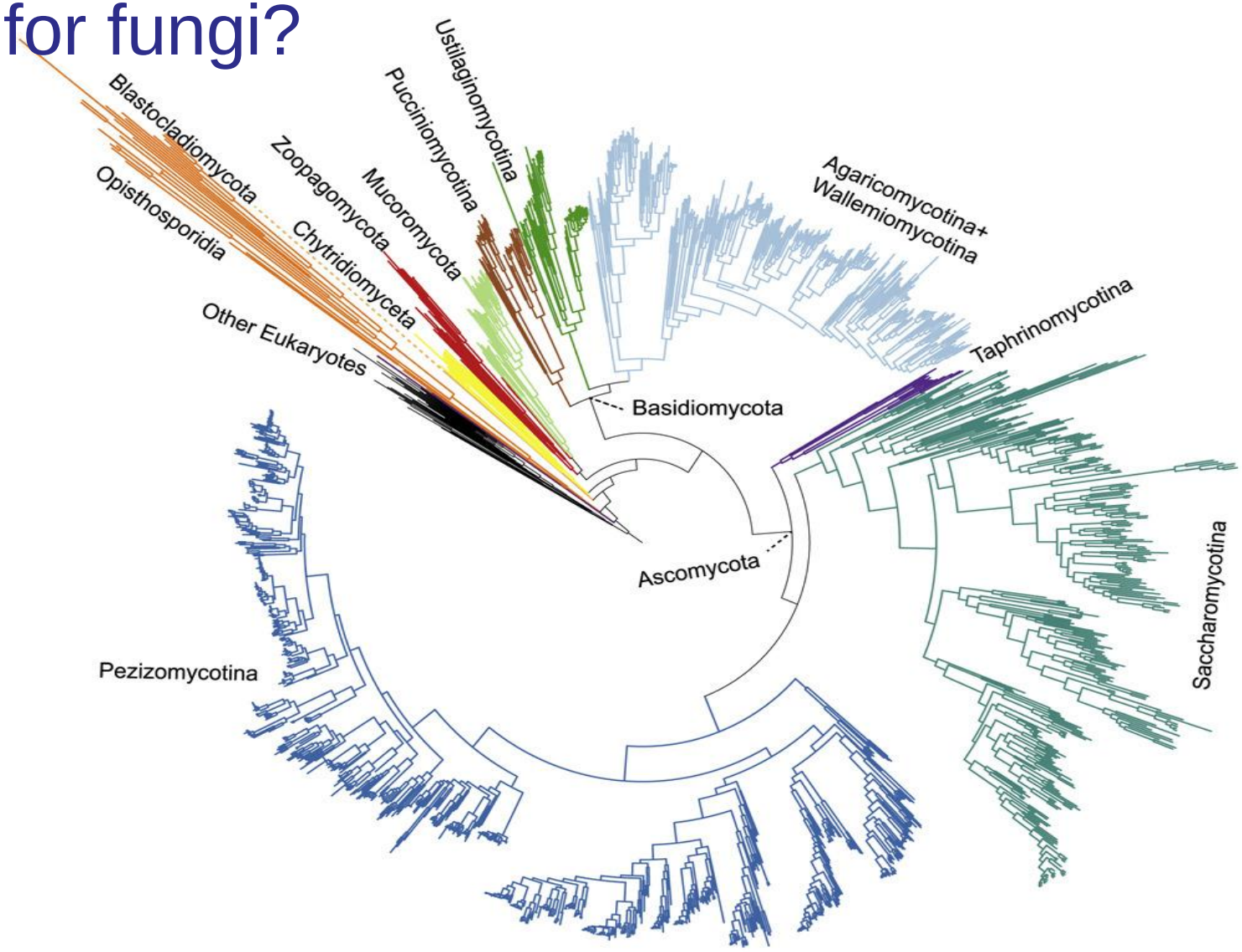
Rossow *et al., J. Fungi* **2020**, https://www.idse.net/Tag/Trichophyton-indotineae/18155; https://www.health.com/condition/infectious-diseases/superbug-fungus-candida-auris; https://www.flickr.com/photos/scotnelson/19353383034; https://www.timeslive.co.za/news/sci-tech/2018-01-25-deadly-fungus-found-in-the-western-cape/

Dramatic ecology alterations - Triple Planetary Crisis

- Climate change
- Pollution
- Biodiversity loss

Why is this relevant for fungi?

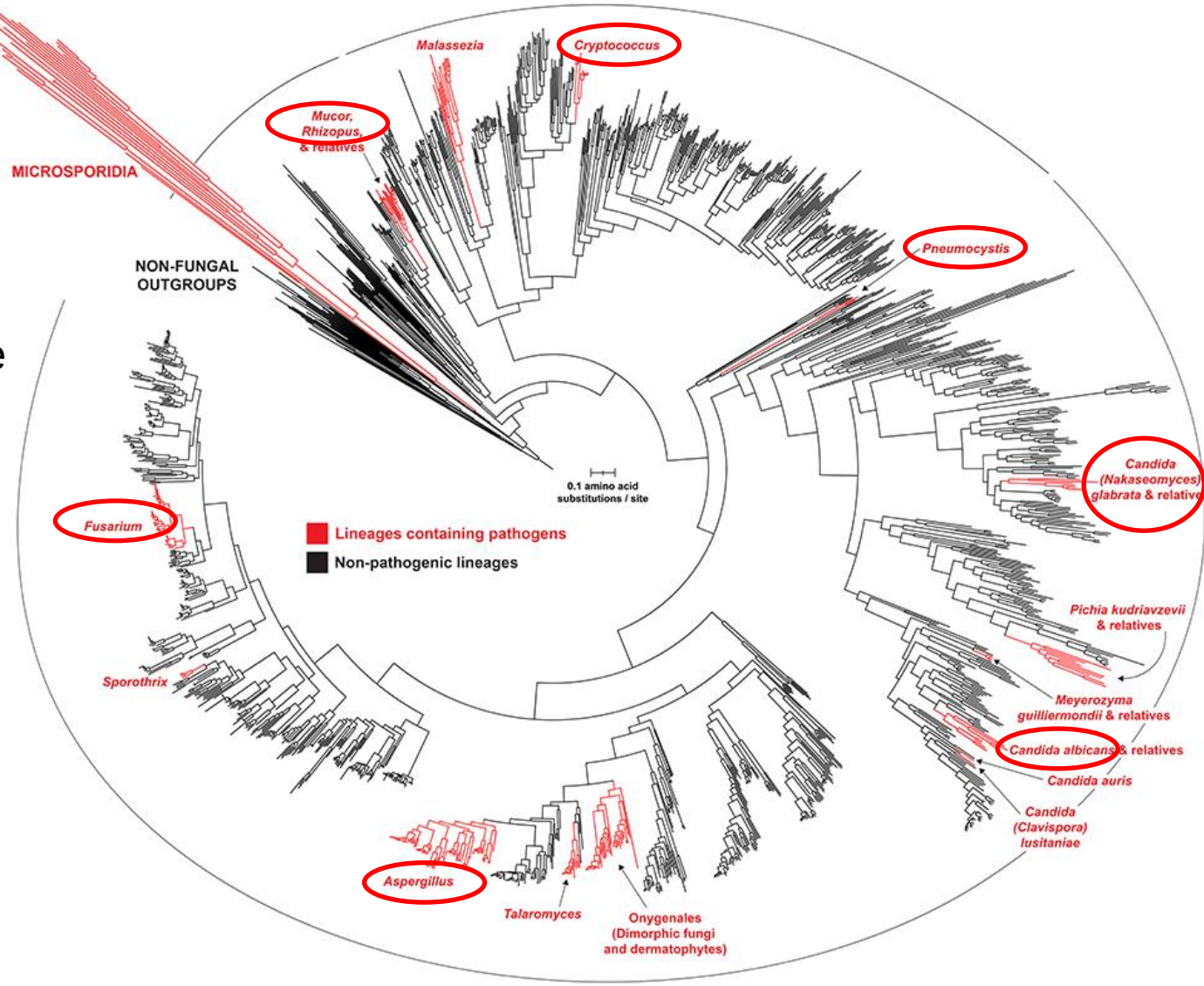
- Estimated 1-5 Mio. species



Rokas *et al.*, Nat. Microbiol 2022

Why is this relevant for fungi?

- Estimated 1-5 Mio. species
- Virulence has evolved everywhere in the fungal kingdom
- Association to warm-blooded hosts is rare in fungi compared to bacteria / viruses



Rokas *et al.*, Nat. Microbiol 2022

A changing world of fungal infections –

What can we do?

- Epidemiology (ID, susceptibility testing, typing)
- New antifungal drugs, new drug targets
- Rational use of antifungals
- Novel therapeutic concepts (personalized medicine, immunotherapy)

HDM-FUN

Acknowledgements

- HDM-FUN consortium
- NRZMyk, funded by the Robert Koch Institute and the Federal Ministry of Health
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- **Aspergillus:** Amelia Barber, Tongta Sae-Ong, Grit Walther, Mohammed Mirhakkak, Sascha Schäuble, Gianni Panagiotou & team
- Images on slides 3, 8, 16-18, 25-27 have been created using BioRender (biorender.com)