

At yeast there is hope, right? Case studies of fungal antimicrobial resistance

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Mycotic Diseases Branch

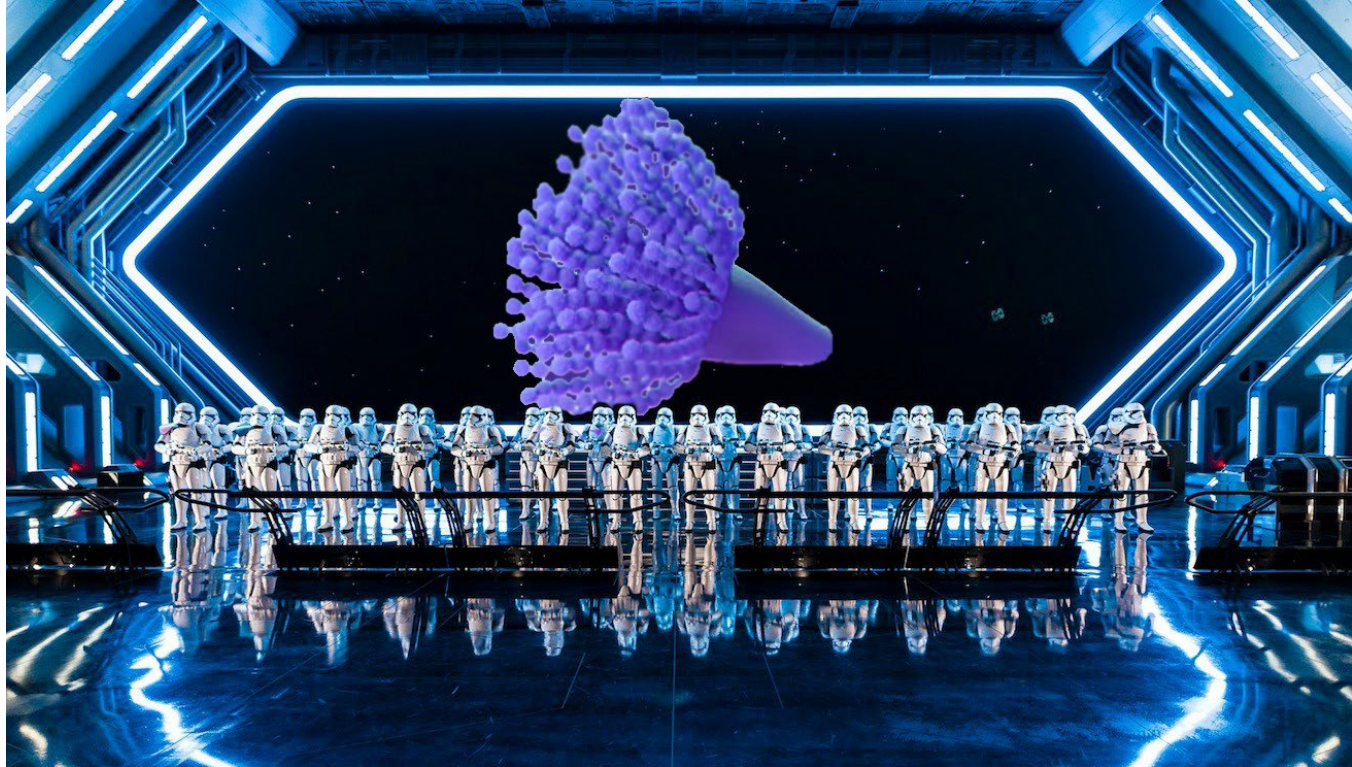
Centers for Disease Control and Prevention

ID Lab Con 2023

3/14/2023



The Rise of the Resistance



Case 1 -

Case History

- Patient reported to Wall Hospital with 2-week history of low-grade fever, shortness of breath and chest pains
- Past medical history includes recent cardiac arrest, and multiple perforated organs
- Patient self-reported he had a new heart (history murky)

Case History

- Patient reported spending a considerable amount of time outdoors
- A large garden was near his home and he reported that his house was filled with dust
- He lived with a single large canine

Case patient

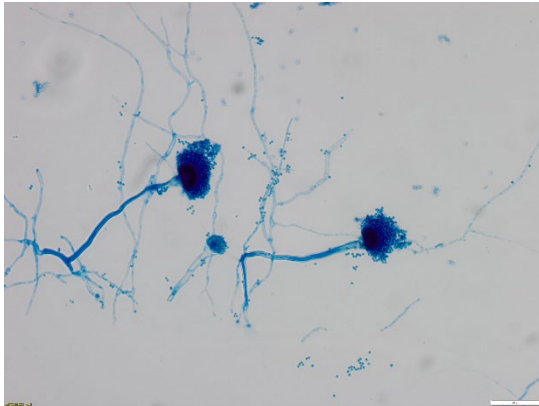


Case History

- Serum galactomannan was positive and *A. fumigatus* was grown from a BAL
- Patient started on voriconazole



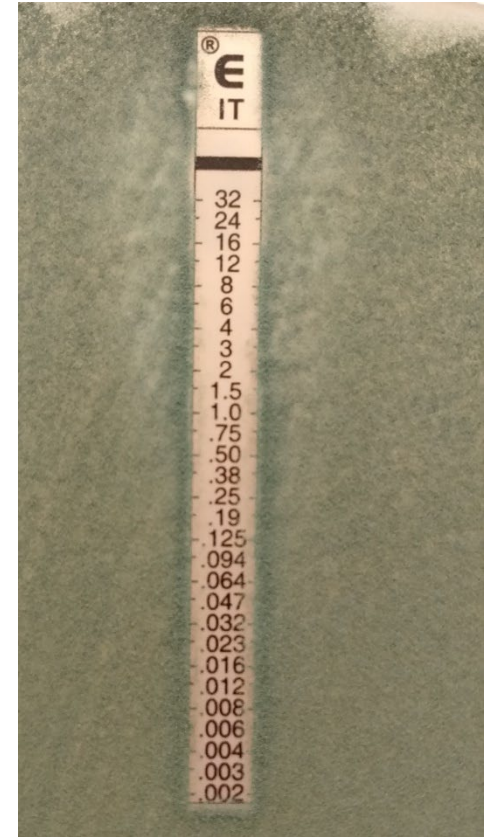
Aspergillus fumigatus and invasive aspergillosis



- Most common invasive mold infection
- High mortality
- Generally immunocompromised patients
- No US surveillance, not reportable or notifiable

Case History

- Symptoms were not resolving following 2 weeks on voriconazole
- AFST was performed and the isolate was pan-azole resistant



Watch List

CDC's Watch List includes three threats that are uncommon, or the full burden of these germs is not yet understood in the United States. There is the potential for these resistant germs to spread across borders and cause significant morbidity and mortality. CDC and other public health experts are closely monitoring these germs, which have the potential to be included as listed threats in the future. Early detection of resistant germs within the United States, followed by implementation of prevention strategies, could reduce spread and public health impact.

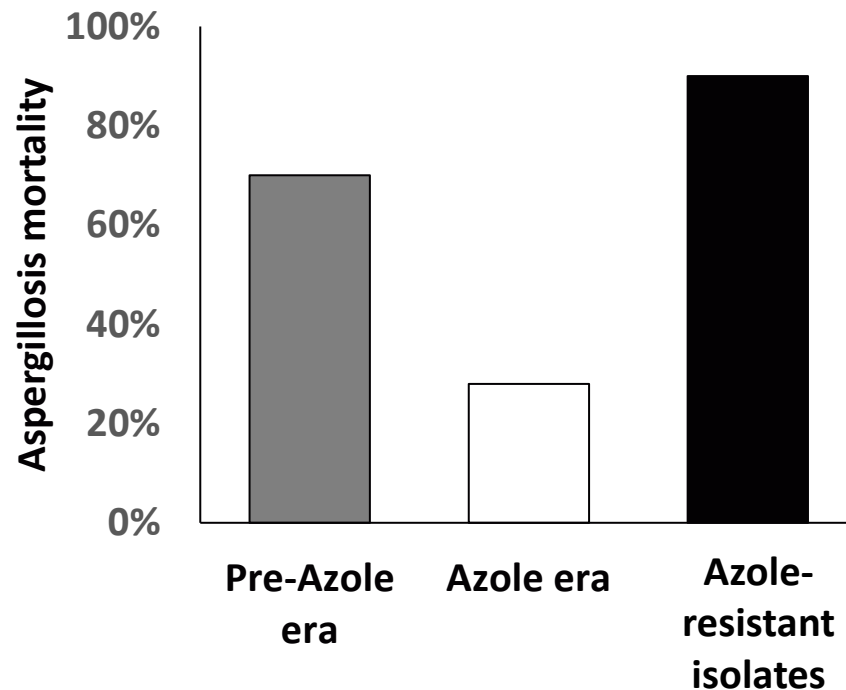


AZOLE-RESISTANT ***ASPERGILLUS FUMIGATUS***

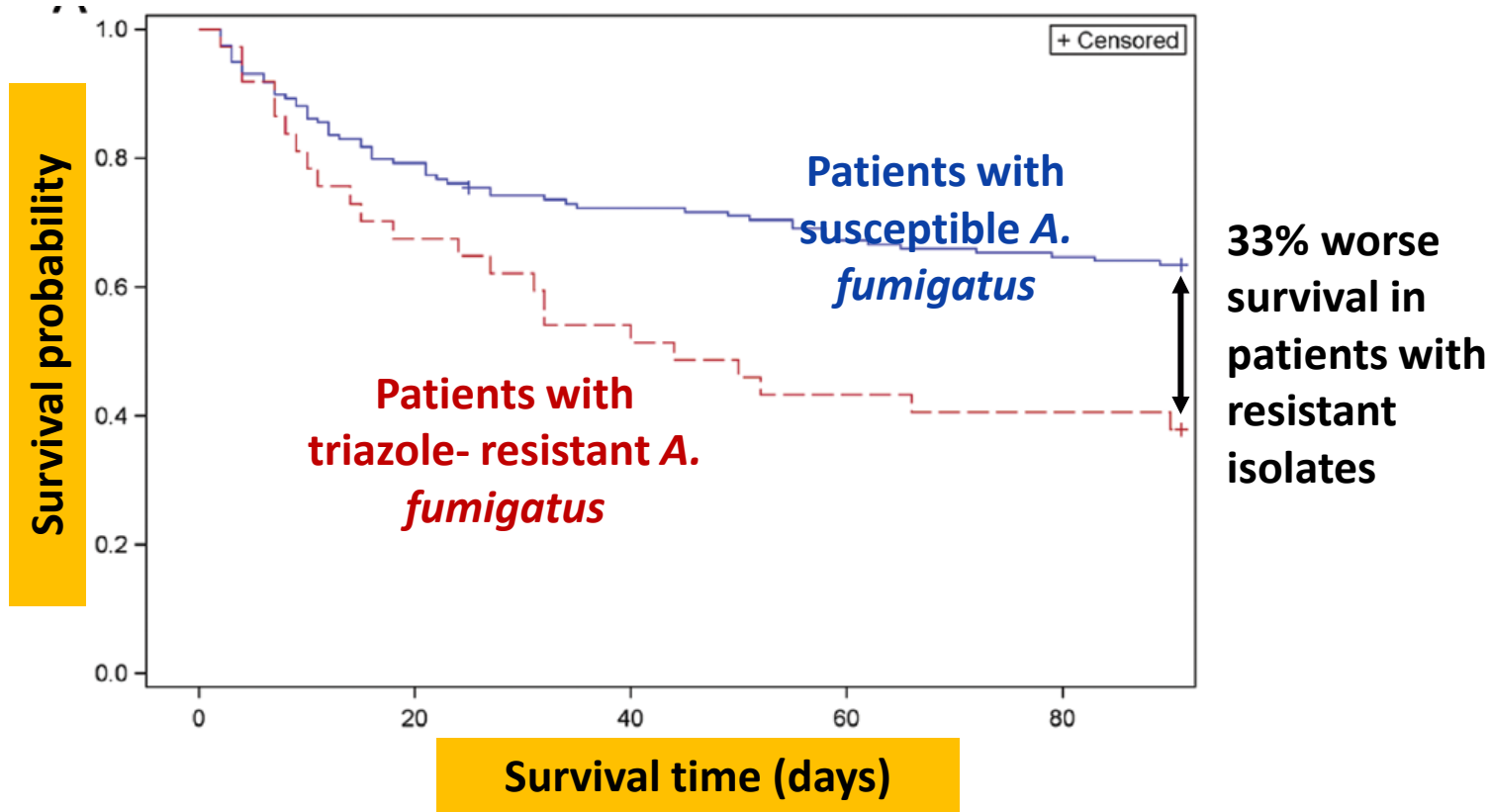
Aspergillus fumigatus is a fungus that can cause life-threatening infections in people with weakened immune systems. These infections are treated with antifungals called azoles. Azoles are also increasingly used in agriculture to prevent and treat fungal diseases in crops. Azole use in human medicine and agriculture can contribute to resistance to antifungal medicines. Although few infections caused by azole-resistant *A. fumigatus* have been identified in the United States, many more infections have been reported in other countries. *A. fumigatus* is challenging to detect because symptoms are similar to many other respiratory infections. When *A. fumigatus* is identified as the cause of an infection, most U.S. laboratories do not have the capability to test for resistance. CDC currently has limited tracking for *A. fumigatus* infections, but CDC is working to better understand how common these infections are and identify the best prevention strategies.

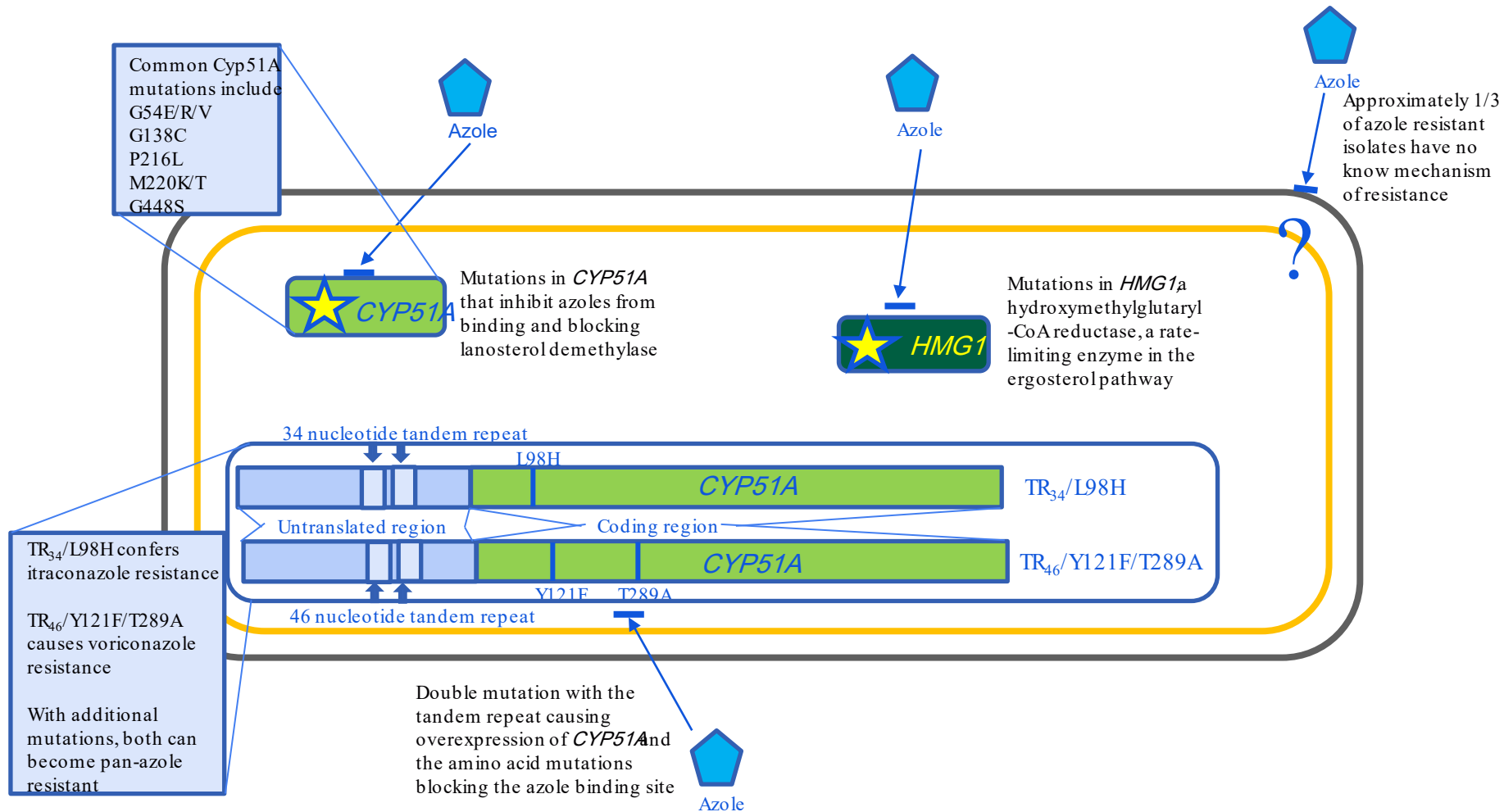
Azole-resistance = high mortality

- Azole antifungals introduced in the 1990s (azole era)
- Dramatically improved survival
- Resistance now a major problem in Europe; seen globally
- Mortality approaches 90% for resistant infections

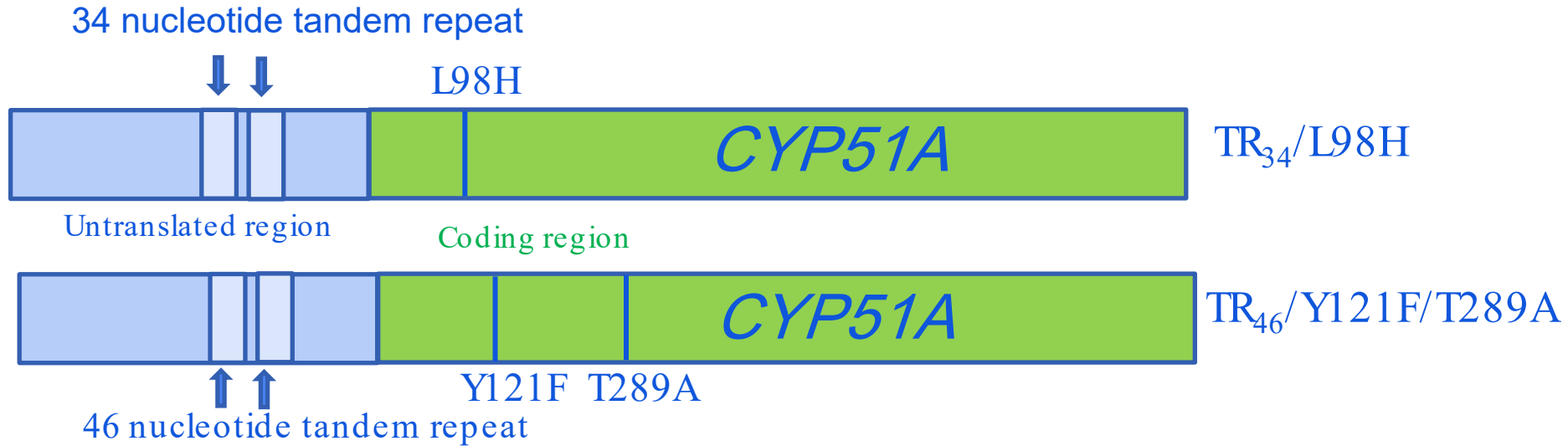


Emerging triazole resistance is deadly





Primary mechanism of resistance



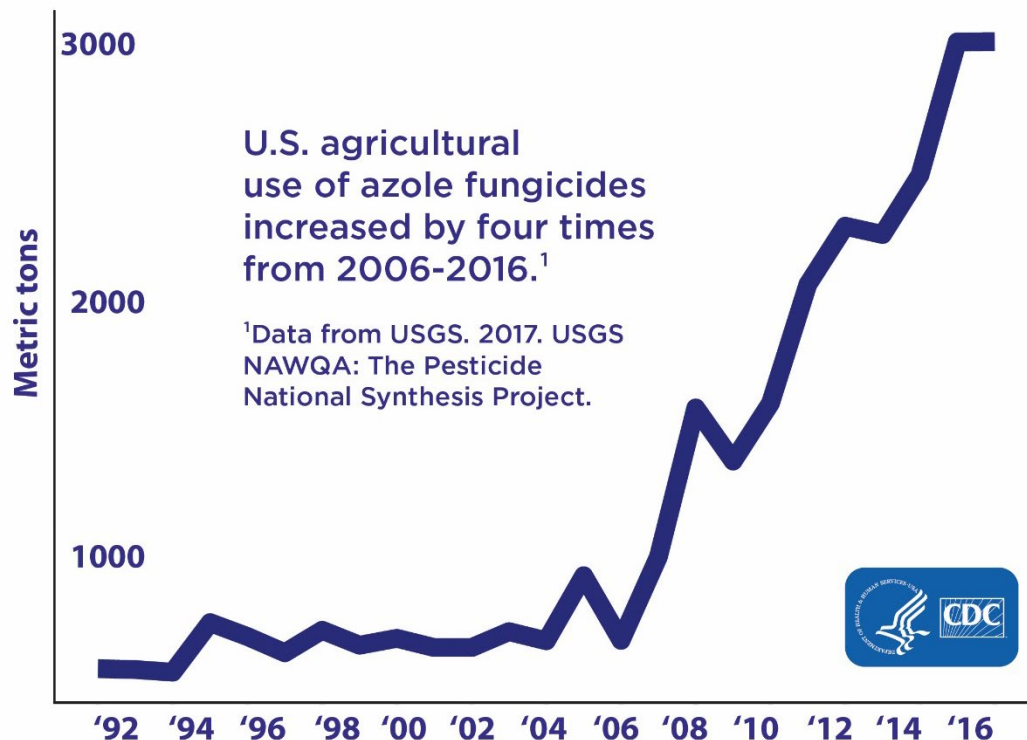
TR₃₄ and TR₄₆

How *Aspergillus fumigatus* became resistant

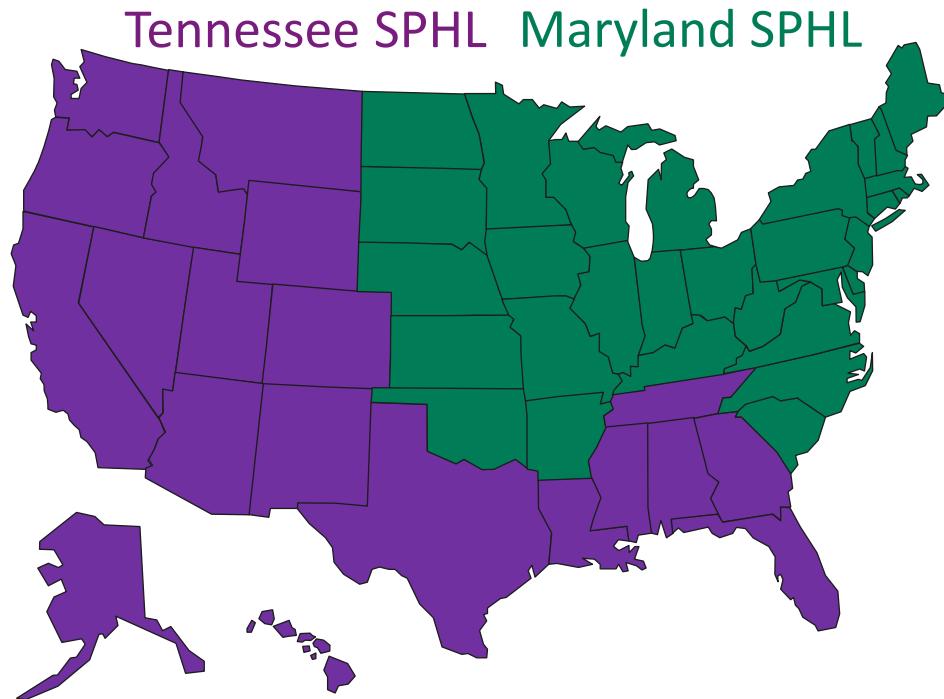
In the Environment



Over four-fold increase in agricultural azole fungicide use in United States



You can have your *A. fumigatus* isolates tested at an ARLN lab for free!



Submit
through your
state public
health lab

New Antifungals in Phase 2/3 trials

Company	Drug	Class or Activity
Mycovia	oteseconazole	Lanosterol demethylase inhibitor
Amplyx	manogepix	Targets GPI anchored protein synthesis
F2G	olorofim	Targets pyrimidine synthesis thru dihydroorotate dehydrogenase

Case 2 -

Case History

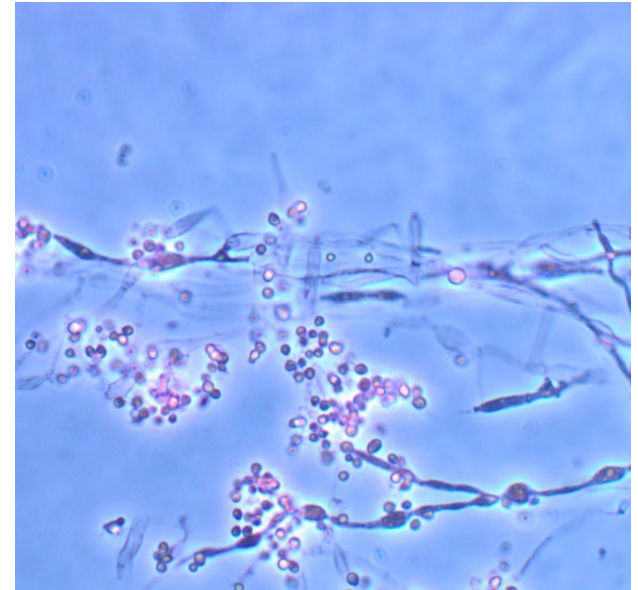
- Patient reported to his dermatology clinic with a 6 week history of burning and itching rash on the back of his torso
- He reported that he often engages in sports where there is skin to skin contact with other athletes
- He had purchased a salve, but it seemed to be making the infection worse

Case patient



Case History

- Punch biopsy grew a white mold
- Microscopy revealed a hyaline mold with round aleuroconidia
- Urease was positive
- Mold was sent to a reference laboratory



Case History

- Reference laboratory identified *Trichophyton mentagrophytes* sequence type VIII
- Patient was prescribed terbinafine
- Three weeks later, patient returned to the clinic because the lesions were not getting better

Typical dermatophytosis





Concise Communication

Terbinafine-resistant strain of *Trichophyton interdigitale* strain isolated from a tinea pedis patient

Junichiro Hiruma, Hiroyuki Kitagawa, Hiromitsu Noguchi, Rui Kano ✉, Masataro Hiruma, Hiroshi Kamata, Kazutoshi Harada

First published: 15 February 2019 | <https://doi.org/10.1111/1346-8138.14809> | Citations: 28

Case Reports | J Dermatol. 2020 May;47(5):e192-e193. doi: 10.1111/1346-8138.15300.

Epub 2020 Mar 10.

Caution and warning: Arrival of terbinafine-resistant *Trichophyton interdigitale* of the Indian genotype, isolated from extensive dermatophytosis, in Japan

Utako Kimura ^{1,2}, Masataro Hiruma ², Rui Kano ³, Tadahiko Matsumoto ^{2,4}, Hiromitsu Noguchi ^{2,4}, Kenji Takamori ¹, Yasushi Suga ¹



Journal de Mycologie Médicale
Volume 29, Issue 4, December 2019, Pages 352-355



Case report

A new mutation in the SQLE gene of *Trichophyton mentagrophytes* associated to terbinafine resistance in a couple with disseminated tinea corporis

A. Hsieh ^a, S. Quenan ^a, A. Riat ^b, L. Toutous-Trellu ^a, L. Fontao ^{a, b} ✉

Emergence of Terbinafine Resistant *Trichophyton mentagrophytes* in Iran, Harboring Mutations in the Squalene Epoxidase (SQLE) Gene

Simin Taghipour, Forough Shamsizadeh, [...], and

Mahdi Abastabar

> Fungal Genet Biol. 2019 Dec;133:103266. doi: 10.1016/j.fgb.2019.103266. Epub 2019 Sep 3.

A unique multidrug-resistant clonal *Trichophyton mentagrophytes*/*Trichophyton interdigitale* complex causing an ongoing alarming dermatophytosis outbreak in India: Genomic insights and resistance profile

Ashutosh Singh ¹, Aradhana Masih ¹, Juan Monroy-Nieto ², Pradeep Kumar Singh ¹, Jolene Bowers ², Jason Travis ², Ananta Khurana ², David M Engelthaler ², Jacques F Meis ⁴, Anuradha Chowdhary ⁵

Infection (2020) 48:889–897

<https://doi.org/10.1007/s15010-020-01498-1>

ORIGINAL PAPER



Intrinsic resistance to terbinafine among human and animal isolates of *Trichophyton mentagrophytes* related to amino acid substitution in the squalene epoxidase

Dominik Łagowski ¹ ✉ · Sebastian Gnat ¹ ✉ · Aneta Nowakiewicz ¹ ✉ · Marcelina Osipińska ¹ ✉ · Mariusz Dyląg ² ✉

Molecular Epidemiology and Antifungal Susceptibility of *Trichophyton* Isolates in Greece: Emergence of Terbinafine-Resistant *Trichophyton mentagrophytes* Type VIII Locally and Globally

by Maria Siopi ¹ ✉, Ioanna Efsthathiou ¹ ✉, Konstantinos Theodoropoulos ² ✉, Spyros Pournaras ¹ ✉ and Joseph Meletiadis ^{1,*} ✉

➤ [Mycopathologia](#). 2020 Dec;185(6):947-958. doi: 10.1007/s11046-020-00455-8. Epub 2020 May 24.

Trichophyton indotineae sp. nov.: A New Highly Terbinafine-Resistant Anthropophilic Dermatophyte Species

Rui Kano¹, Utako Kimura², Maki Kakurai³, Junichiro Hiruma⁴, Hiroshi Kamata⁵, Yasushi Suga², Kazutoshi Harada⁴

Affiliations + expand

PMID: 32449054 DOI: [10.1007/s11046-020-00455-8](#)

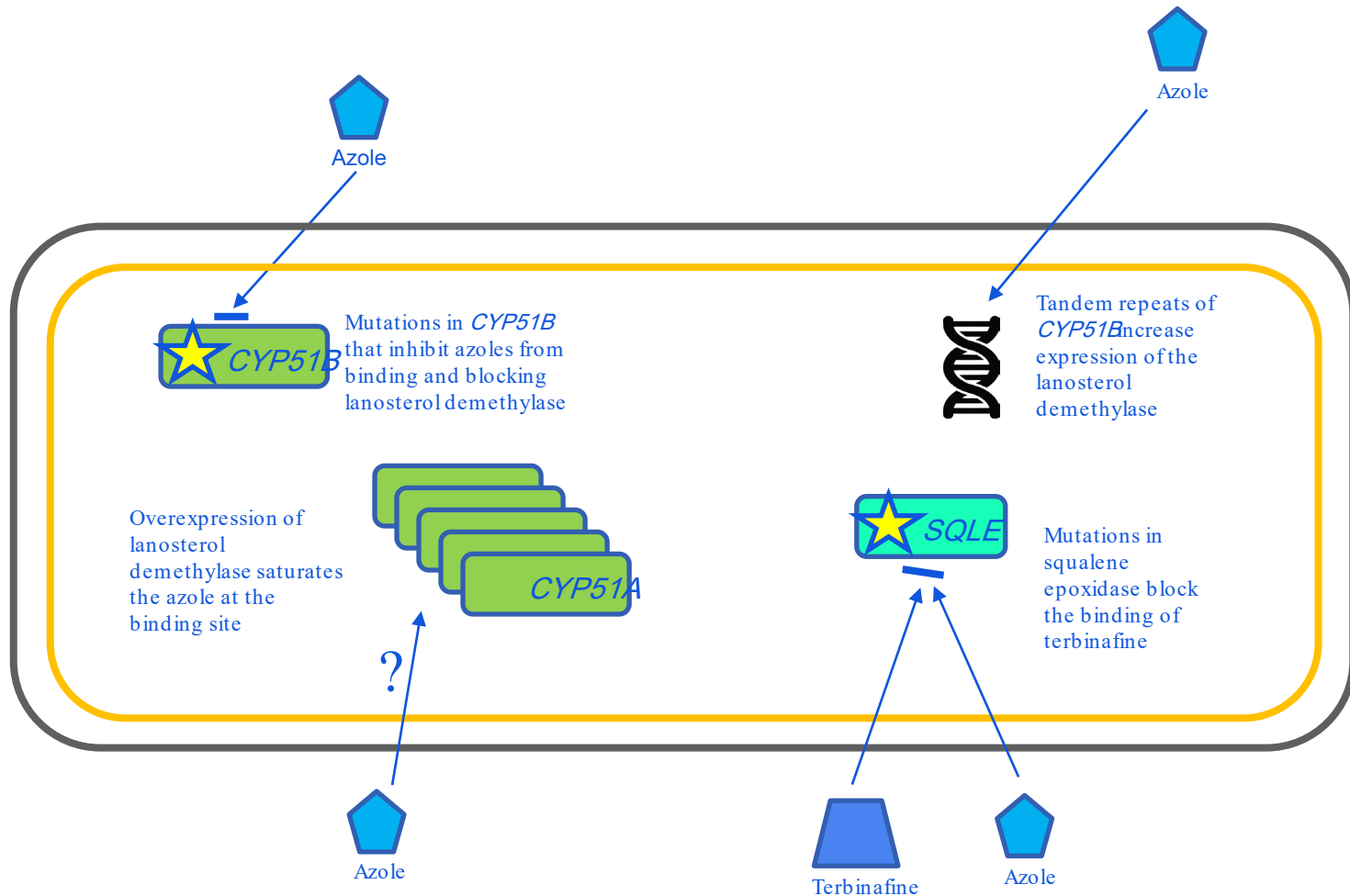
Trichophyton indotinea infection

- Extensive chronic relapsing infection of the trunk and groin
- More severe infection compared with *T. mentagrophytes* and *T. interdigitale*
- Many infections are highly inflammatory, cover much or all the lower body and groin, and can extend to the extremities and head.
- Often associated with painful burning and itching and can cause significant morbidity

Steroid-modified Dermatophytosis

- Concerns regarding steroid-modified tineas with improper drug usage
- Common to obtain over-the-counter medications
- Atypical presentation





Trichophyton indotineae in the US

- As for most fungal infections there is no surveillance for dermatophytosis
- Very few labs identify dermatophytes to species almost none perform AFST
- *T. indotineae* has been identified in the US (Nathan Wiederhold, personal communication)
- First signs will be patients failing therapy

Case 3 -

Case History

- 28 year old male reported to the ER after falling from a horse
- In addition to injuries suffered during the fall, he had a facial laceration from a blunt instrument; patient was started on oral antibiotics
- Patient was stabilized and within 5 days he was removed to an acute care facility
- Five days following the admission to the acute care facility the facial wound showed signs of infection

Facial wound of case patient



Case History

- A swab was taken from the wound and among several gram negative organisms, the wound grew abundant yeast that were pinkish on CHROMagar
- Isolate could not be identified at the acute care clinic but their reference laboratory identified it as *C. auris*



Urgent Threats

These germs are public health threats that require urgent and aggressive action:



CARBAPENEM-RESISTANT
ACINETOBACTER



CANDIDA AURIS



CLOSTRIDIoidES DIFFICILE



CARBAPENEM-RESISTANT
ENTEROBACTERIACEAE



DRUG-RESISTANT
NEISSERIA GONORRHOEAE

What do we know about *Candida auris*?

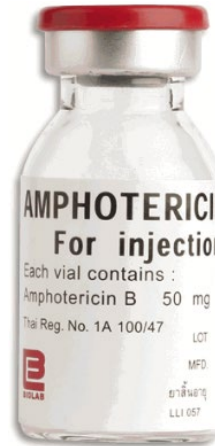
- It colonizes the skin
- It is most antifungal resistant
- In the US, associated with LTACHs, VSNFs
- Frequently causes outbreaks



Resistance in *Candida auris*



85%
Azoles



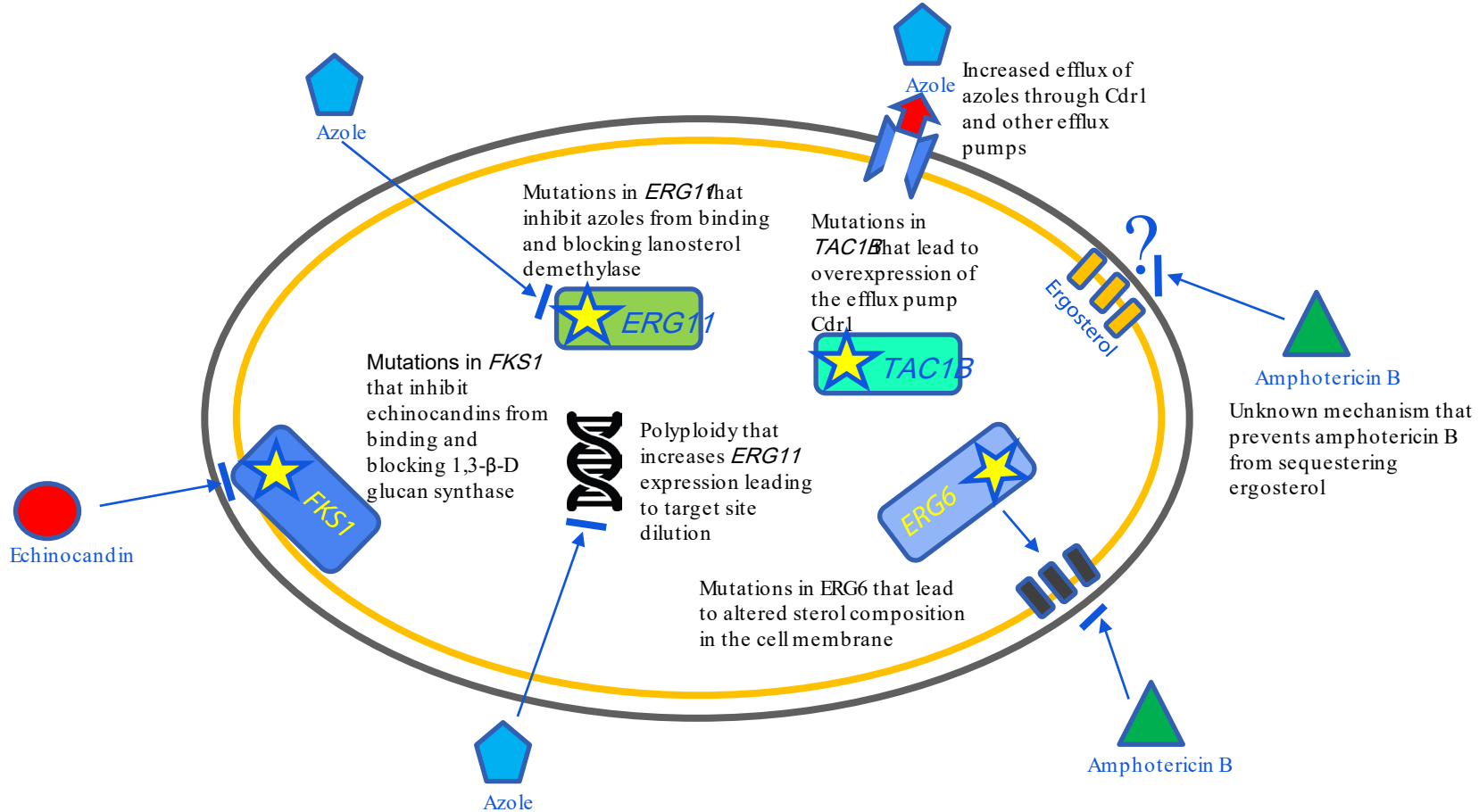
31%
Polyenes



4%
Echinocandins

~30% are multidrug resistant

Many different methods of acquiring resistance



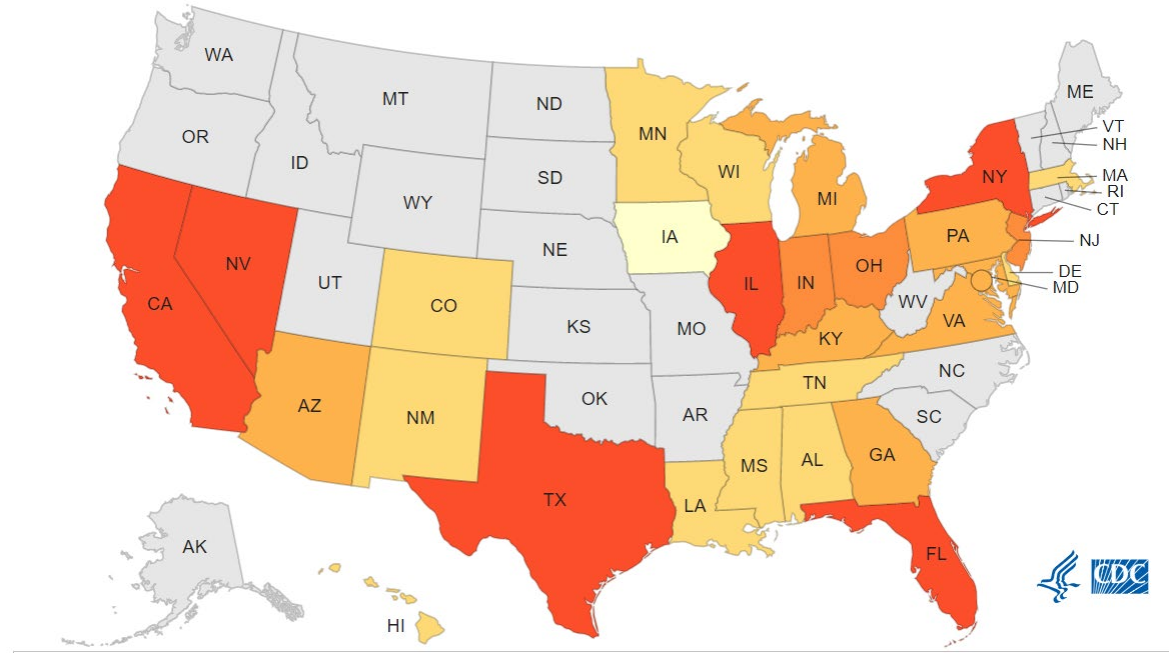
Fitness cost?

Morbidity and Mortality Weekly Report *Notes from the Field*

Transmission of Pan-Resistant and Echinocandin-Resistant *Candida auris* in Health Care Facilities — Texas and the District of Columbia, January–April 2021

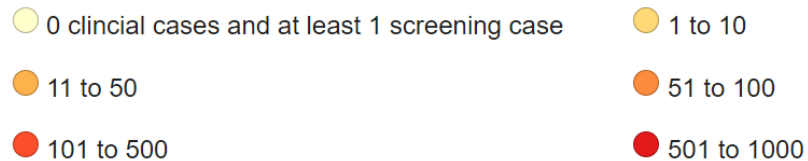
Meghan Lyman, MD¹; Kaitlin Forsberg, MPH¹; Jacqueline Reuben, MHS²; Thi Dang, MPH³; Rebecca Free, MD¹; Emma E. Seagle, MPH¹; D. Joseph Sexton, PhD¹; Elizabeth Soda, MD⁴; Heather Jones, DNP⁴; Daryl Hawkins, MSN²; Adonna Anderson, MSN²; Julie Bassett, MPH³; Shawn R. Lockhart, PhD¹; Enyinnaya Merengwa, MD, DrPH³; Preetha Iyengar, MD²; Brendan R. Jackson, MD¹; Tom Chiller, MD¹

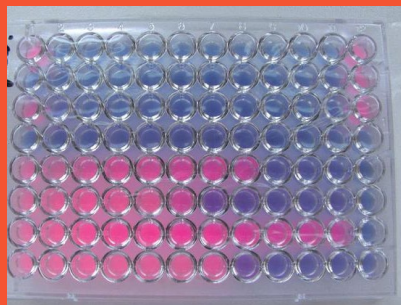
Candida auris in the US



Number of *C. auris* clinical cases through December 31, 2022

In the most recent 12 months, there were 2,377 clinical cases and 5,754 screening cases (January 2022 - December 2022).





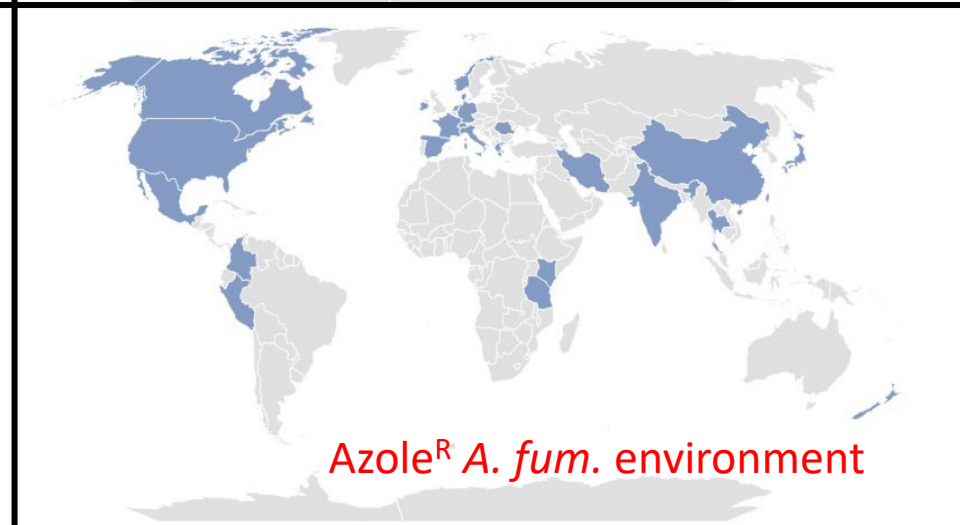
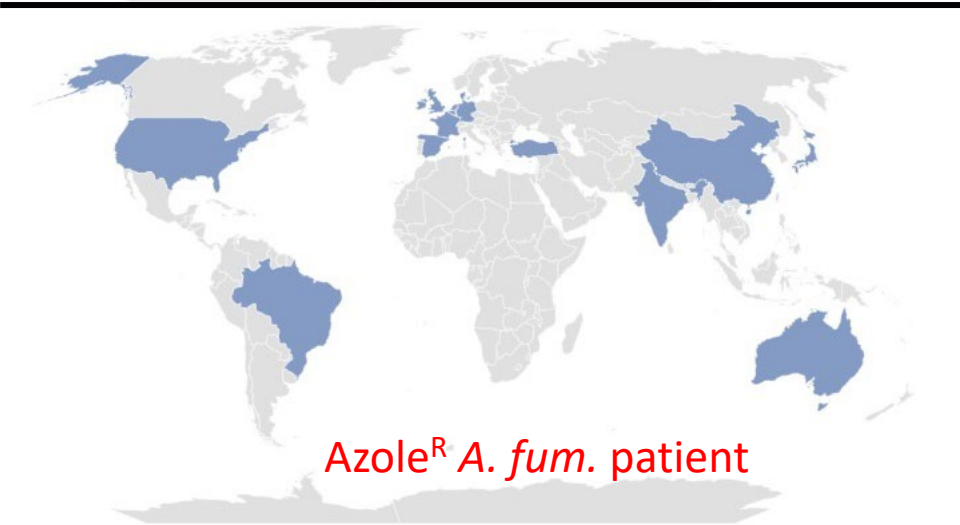
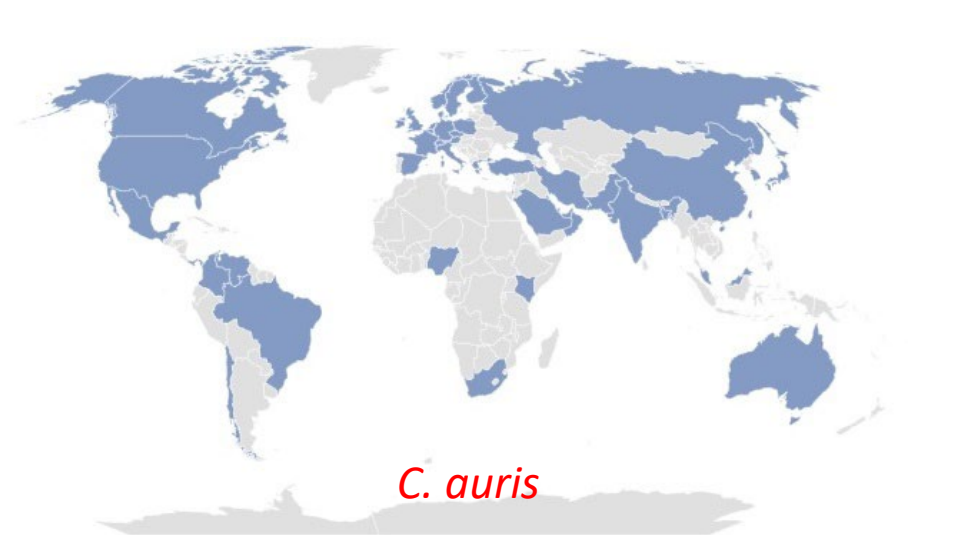
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What do they all have in common?



What's next?



What's next?

- Dramatic rise in azole-resistant *Candida parapsilosis*
- Rise in azole resistant *Candida tropicalis*
- Resistance in other *Aspergillus* species such as *A. flavus*
- Something new and unexpected

Thank you! Questions?



For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

Contact me at:
gyi2@cdc.gov

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

