National Center for Emerging and Zoonotic Infectious Diseases

The Emerging Threat of Antifungal-Resistant *Candida*

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National Academies Workshop
June 20, 2022

Illustrative, hypothetical case

- **61-year-old man** with hypertension and pre-diabetes
- Presents to emergency department in late 2020 with **cough, fever, shortness of breath**, and recent COVID-19 exposure
- Admitted to hospital for **low oxygen levels;** confirmed **SARS-CoV-2 infection**
  - Remdesivir, **dexamethasone, tocilizumab**
  - **Empiric antibiotics** for possible community-acquired pneumonia
- Next day: **rapid worsening**, requiring intubation and ICU admission
- Develops **septic shock**, requiring vasopressors through central line

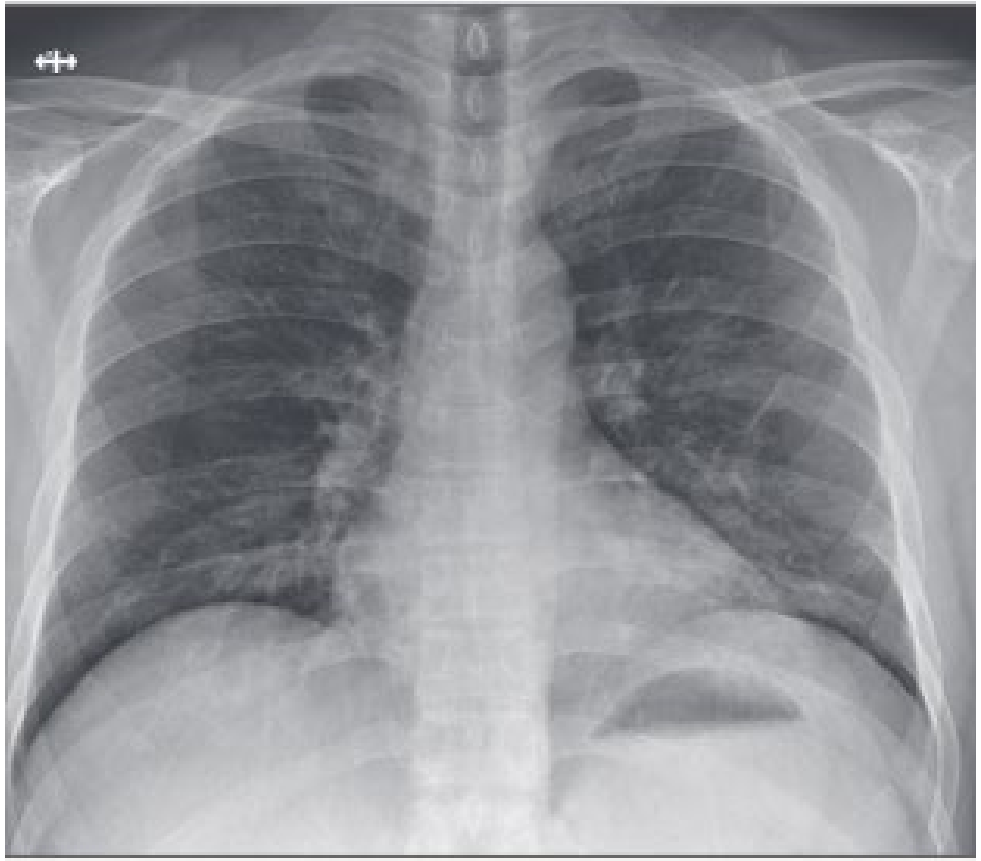


Image Source: First Case of 2019 Novel Coronavirus in the United States (cdc.gov)

Hospital course: improvement followed by rapid deterioration

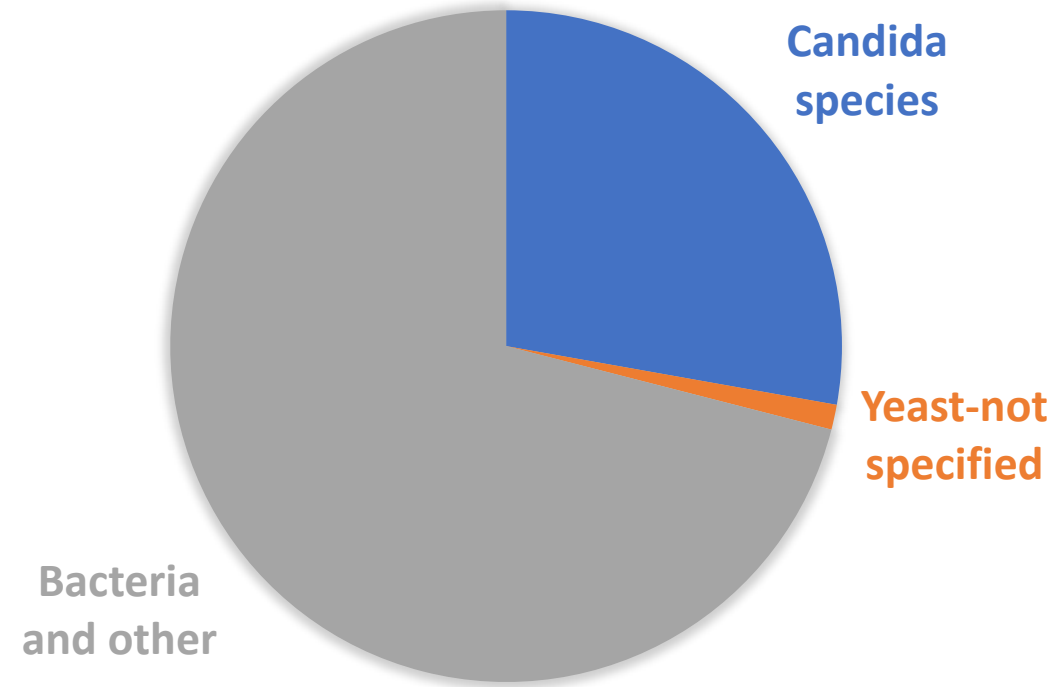
- Day 6: **Improving respiratory status**, fever resolves
- Day 10: **new fever**, drop in blood pressure
  - **Broader antibiotics** for possible healthcare-associated infection
- Day 12: Blood cultures return with ***Candida*** species; still doing poorly
  - **Fluconazole** added
- Day 13: Identified as ***Candida glabrata*** **resistant to fluconazole**
  - Fluconazole changed to **echinocandin**
- Day 16: **Patient's outcome?**

This is not rare! *Candida* species a leading cause of healthcare-associated bloodstream infections, irrespective of pandemic

In U.S. data from 2020, ***Candida*** **caused**

- **28%** of central line-associated bloodstream infections (CLABSI) in **ICUs**
  - Most common bacteria: 18%
- **13% of CLABSIs in adult wards**
  - Most common bacteria: 12% (*S. aureus*)

ICU CLABSI in 2020 by pathogen type



Pathogens attributed to central line-associated bloodstream infections in US acute care hospitals during the first year of the COVID-19 pandemic | Infection Control & Hospital Epidemiology | Cambridge Core

Changes in Prevalence of Health Care–Associated Infections in U.S. Hospitals | NEJM

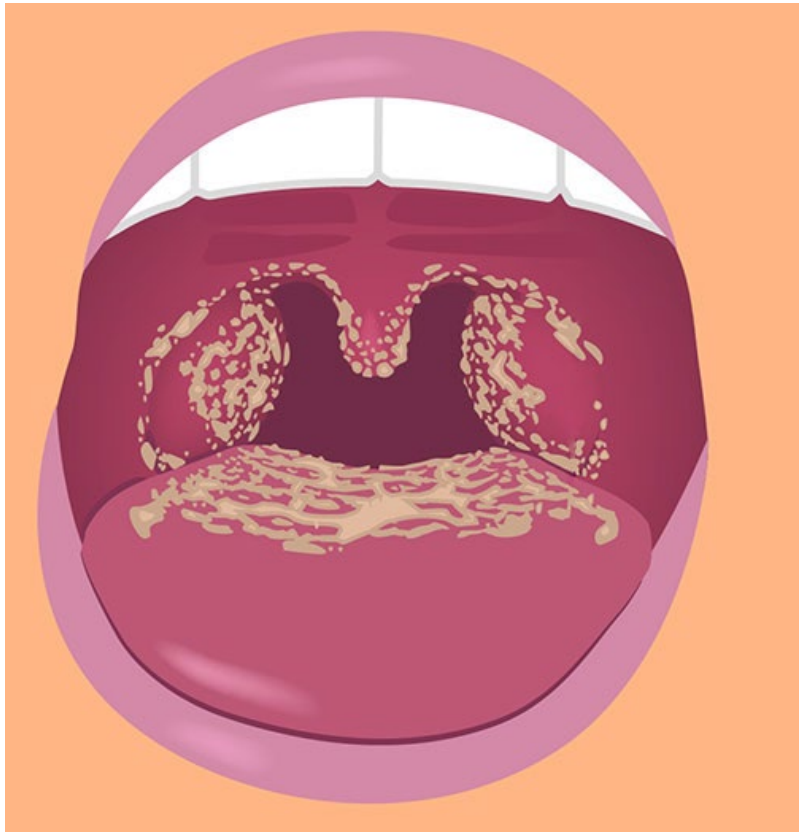
About *Candida* bloodstream infections (candidemia)

- **>25-30% mortality rate**, with 10-25% attributable mortality (according to Dr. Spec)
- **Risk factors** include
  - Broad-spectrum antibiotic use
  - Central lines
  - Immunocompromise
  - Prolonged ICU stay
  - Abdominal surgery
- **Deep-seated *Candida* infections** (i.e., internal organs) may be nearly as common but harder to detect and monitor
- **Conventional wisdom**: autoinfection with host flora, particularly from gut

Image credit: Human Microbiome Project - Home | NIH Common Fund

Substantial morbidity from non-invasive candidiasis

- Types include
  - Vulvovaginal (“yeast infections”)
  - Oral (“thrush”)
  - Esophageal
  - Skin infections
- **>3.6 million estimated outpatient visits** in 2017
- **>$2 billion** in direct medical costs
- Likely reason for vast majority of systemic azole therapy

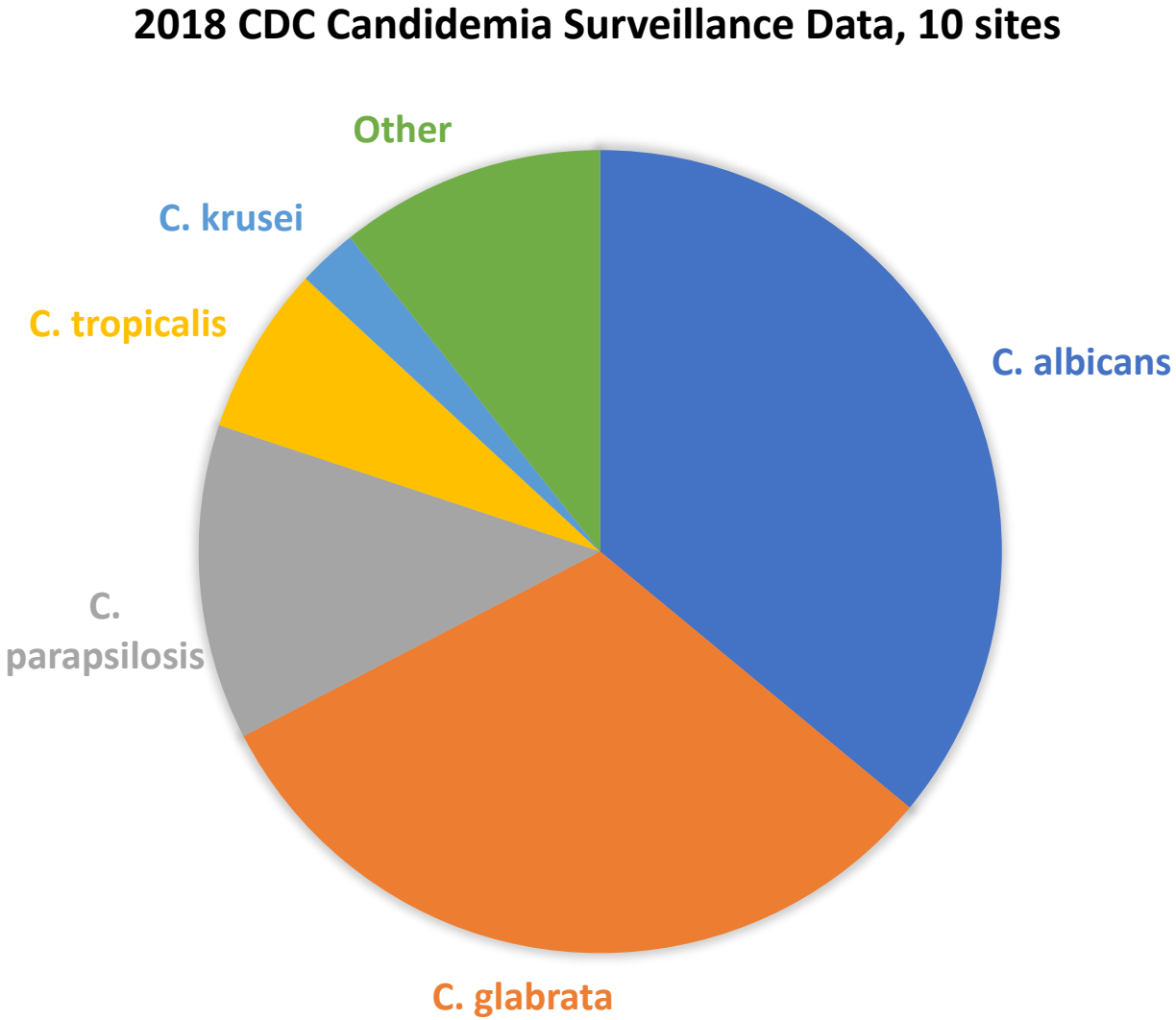


Estimation of direct healthcare costs of fungal diseases in the United States - PMC (nih.gov)
Outpatient antifungal prescribing patterns in the United States, 2018 | Antimicrobial Stewardship & Healthcare Epidemiology | Cambridge Core

Fall of King Albicans

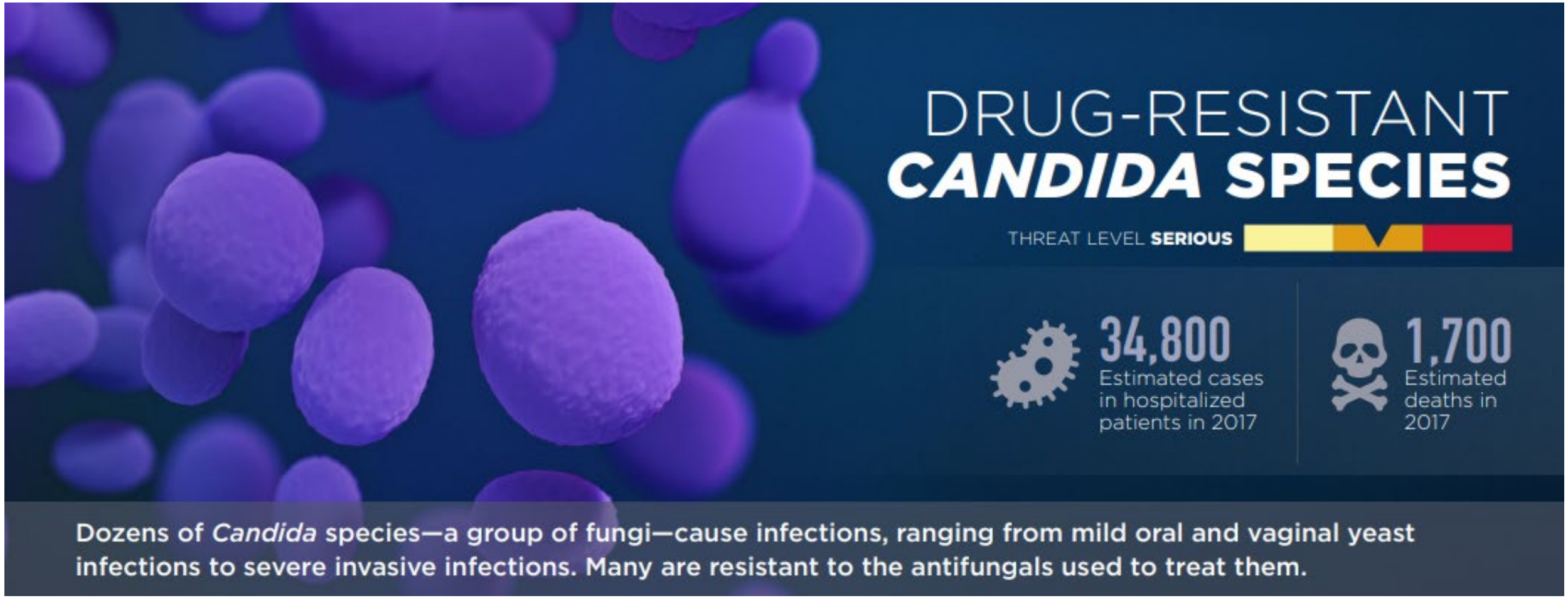
- ***Candida albicans* once the dominant species** causing invasive human infections (~90%)

- Now **two-thirds are non-*albicans***



HAICViz | HAIC Activities | HAI | CDC

Why does it matter?

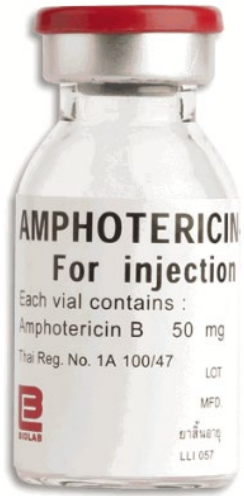


2019 Antibiotic Resistance Threats Report | CDC

C. glabrata resistance to the 3 main antifungal classes for treating invasive candidiasis (2016-2018)

6-10%
Azoles

1-4%
Echinocandins



<1%
Polyenes

HAICViz | HAIC Activities | HAI | CDC
Use of images does not imply endorsement

C. glabrata isn't alone: growing resistance to *C. parapsilosis* and *C. tropicalis;* intrinsic *C. krusei* resistance

- ***C. parapsilosis***: up to 10% fluconazole resistance in US data
- ***C. tropicalis*****:** up to 6% fluconazole resistance in US data
- **Increasing emergence of resistant clones** worldwide of both species

- ***C. krusei:*** usually **intrinsically resistant** to fluconzole

Emergence of azole-resistant Candida parapsilosis causing bloodstream infection: results from laboratory-based sentinel surveillance in South Africa | Journal of Antimicrobial Chemotherapy | Oxford Academic (oup.com)
Resistance of Candida to azoles and echinocandins worldwide – ScienceDirect
Frontiers | Notable Increasing Trend in Azole Non-susceptible Candida tropicalis Causing Invasive Candidiasis in China (August 2009 to July 2014): Molecular Epidemiology and Clinical Azole Consumption | Microbiology (frontiersin.org)

Growing resistance made echinocandins first-line treatment in 2016

GUIDELINES

Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America FREE

Even if uptake is uneven

- 30% received **fluconazole as initial treatment**
  - Over half (56%) **grew a non-*albicans* species**
  - 10% of those with susceptibility testing **had resistant isolates**

Clinical Infectious Diseases

MAJOR ARTICLE

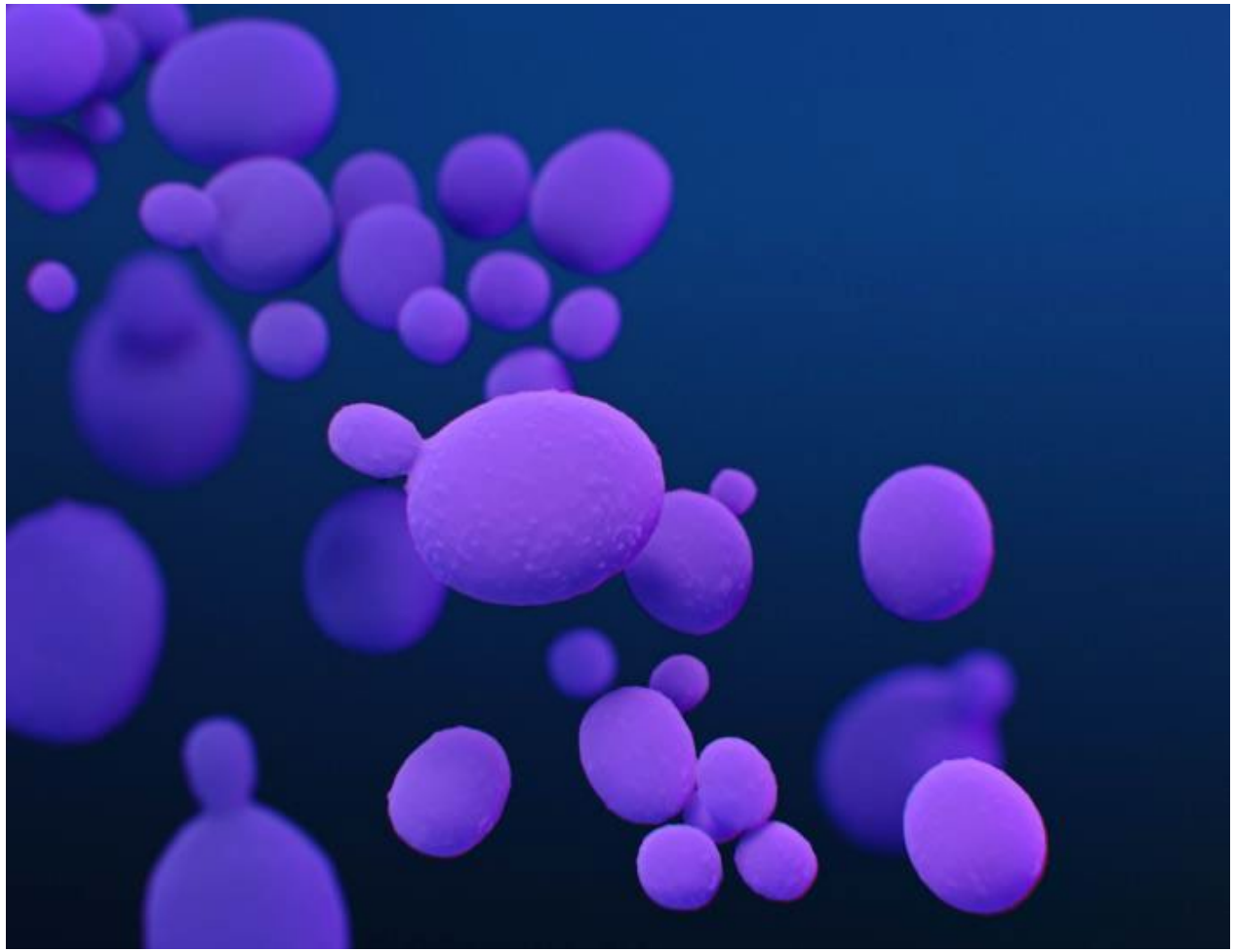
Treatment Practices for Adults With Candidemia at 9 Active Surveillance Sites—United States, 2017–2018

And the World Health Organization to include *Candida* in antimicrobial surveillance

Global Antimicrobial Resistance and Use Surveillance System (GLASS) (who.int)

And then along came *C. auris*

- First described in 2009 from an ear specimen (i.e., *auris*)
- Early 2010s: Not just for ears, as global reports of invasive infections emerge
- Burst on the scene in 2016…



Key press coverage of 2016 CDC alert

A Deadly, Drug-Resistant Yeast Infection Is Spreading Around the World, It's Fine Guys

Me? I'm calm. I'm so calm!

"All the News That's Fit to Print"

The New York Times

Late Edition

Today, sunshine mixing with some clouds, mild, high 64. **Tonight,** cloudy, periodic rain, low 53. **Tomorrow,** a brief shower or two, high 72. Details in SportsSunday, Page 10.

VOL. CLXVIII . . No. 58,290 NEW YORK, SUNDAY, APRIL 7, 2019 $6.00

DADO GALDIERI FOR THE NEW YORK TIMES

A scout discovered Maradoninha, 11, two years ago. His family moved 1,200 miles to enable him to get first-class training.

Fungus Immune to Drugs Quietly Sweeps the Globe

Lethal Infection Adds Alarming Dimension to Dangers of Overusing Medicines

By MATT RICHTEL and ANDREW JACOBS

Last May, an elderly [illegible] admitted to the Brooklyn branch of Mount Sinai Hospital for abdominal surgery. A blood test revealed that he was infected with a newly discovered germ as deadly as it was mysterious. Doctors swiftly isolated him in the intensive care unit.

DEADLY GERMS, LOST CURES
A New Public Health Threat

The germ, a fungus called Candida auris, preys on people with weakened immune systems, and it is quietly spreading across the globe. Over the last five years, it has hit a neonatal unit in Venezuela, swept through a hospital in Spain, forced a prestigious British medical center to shut down its intensive care unit, and taken root in [illegible] example of one of the world's most intractable health threats: the rise of drug-resistant infections.

For decades, public health experts have warned that the overuse of antibiotics was reducing the effectiveness of drugs that have lengthened life spans by curing bacterial infections once commonly fatal. But lately, there has been an explosion of resistant fungi as well, adding a new and frightening dimension to a phenomenon that is undermining a pillar of modern medicine.

"It's an enormous problem," said Matthew Fisher, a professor of fungal epidemiology at Imperial College London, who was a coauthor of a recent scientific review on the rise of resistant fungi.

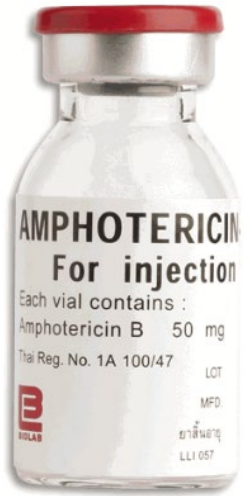
Why we care about a once-obscure yeast: It acts like multidrug-resistant bacteria

- **Spreads readily** in healthcare facilities
- Causes **outbreaks**
- **Colonizes patients**, especially skin, taking advantage of disrupted microbiome
- Causes **invasive infections** in 5-10% of those colonized
- **Contaminates healthcare environments**
- Thumbs its nose at commonly used healthcare **disinfectants**

C. auris resistance makes *C. glabrata* look tame by comparison

~90%
Azoles

<5%
Echinocandins



~33%
Polyenes

HAICViz | HAIC Activities | HAI | CDC
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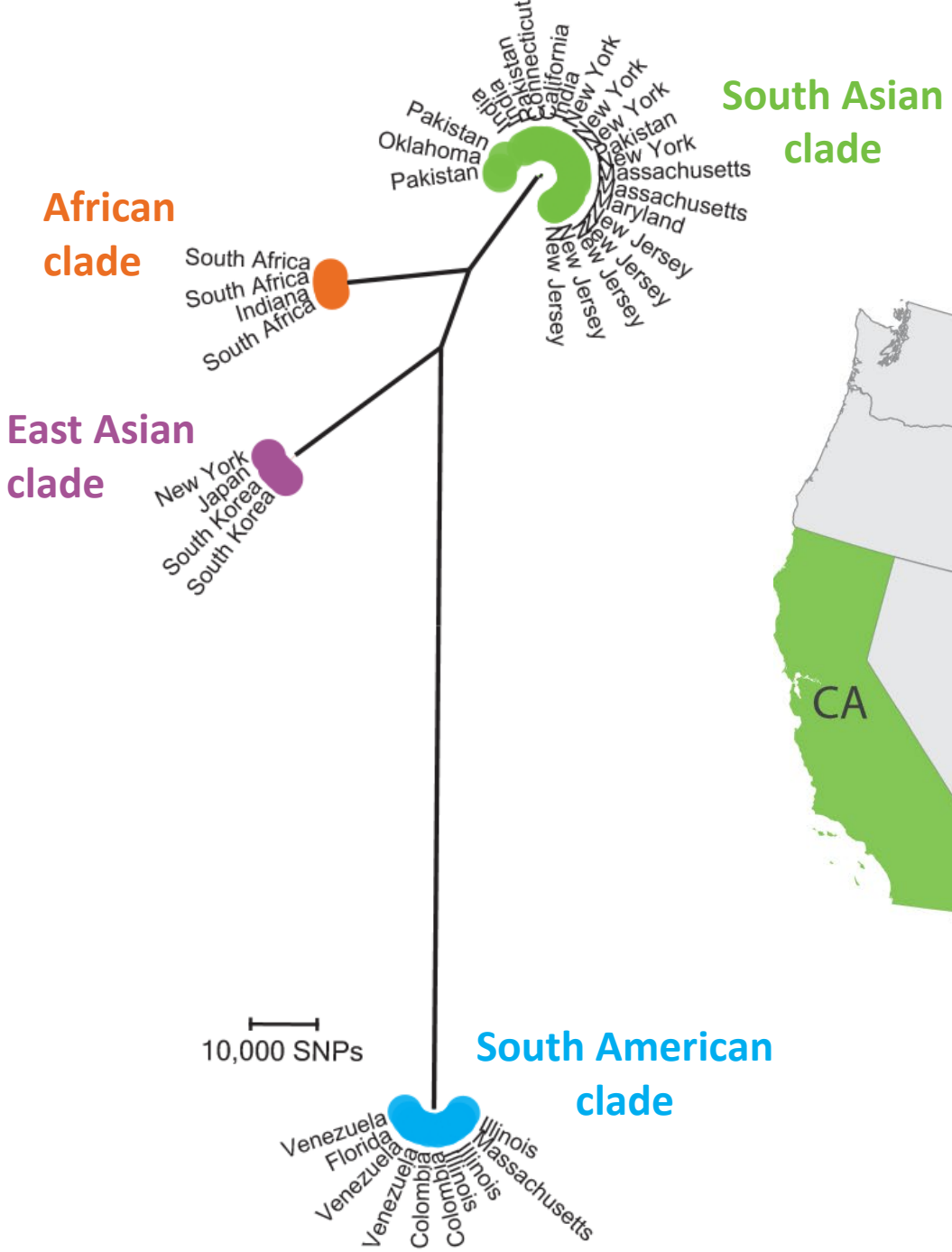
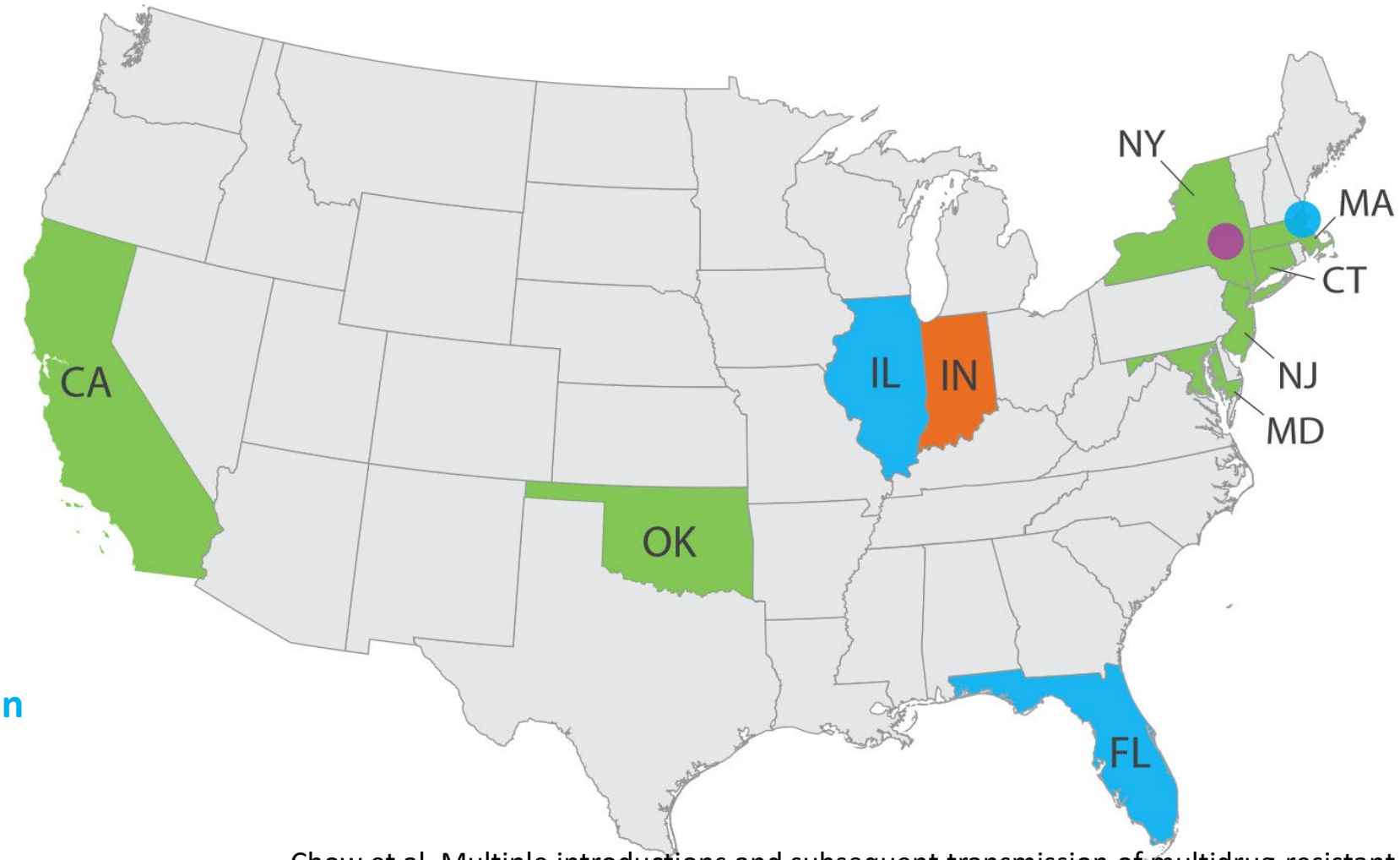
We’re starting to see spread of *C. auris* resistant to all three drug classes

Morbidity and Mortality Weekly Report (*MMWR*)

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

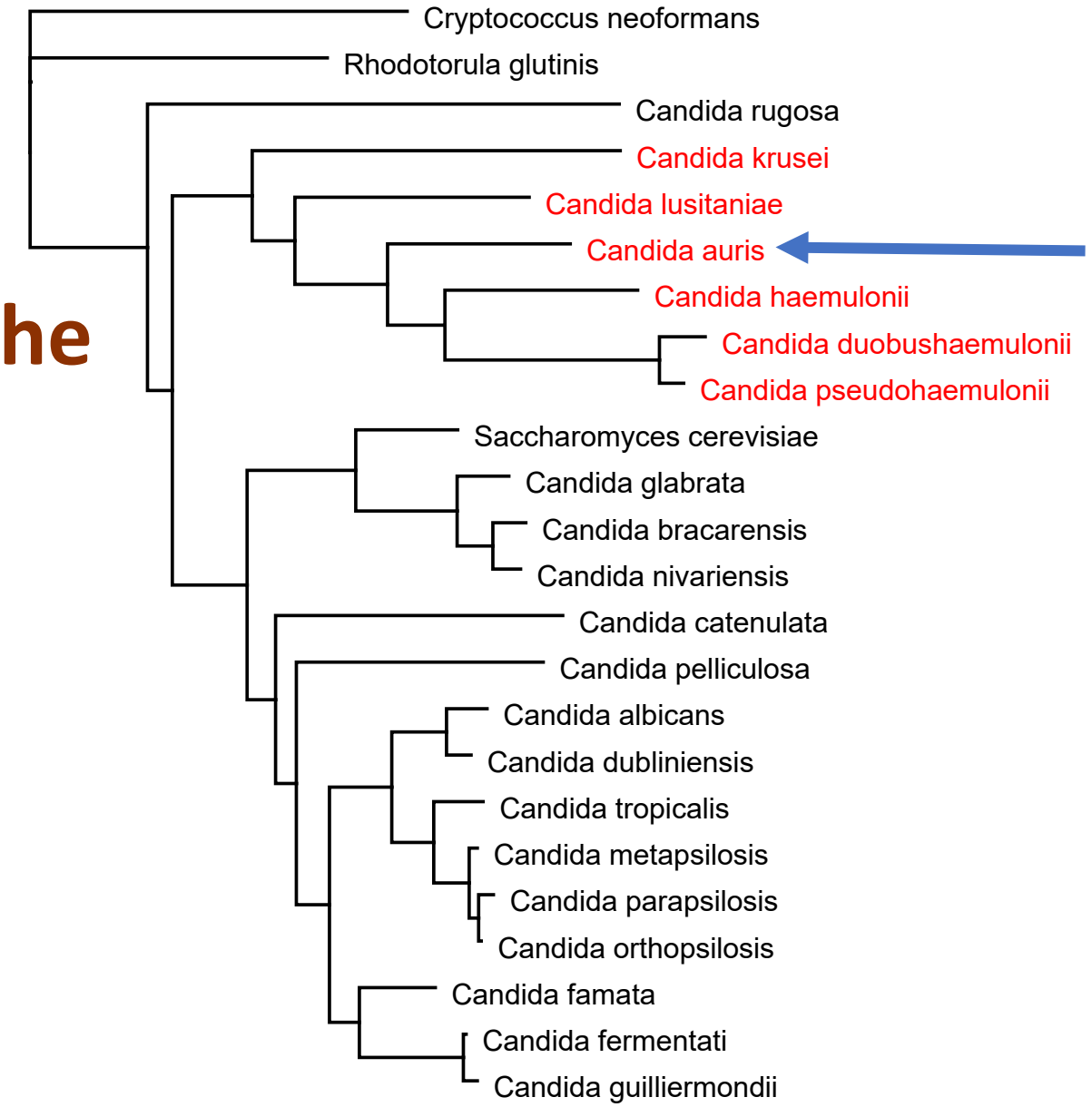
Puzzling finding: At least four genetically distinct *C. auris* clades



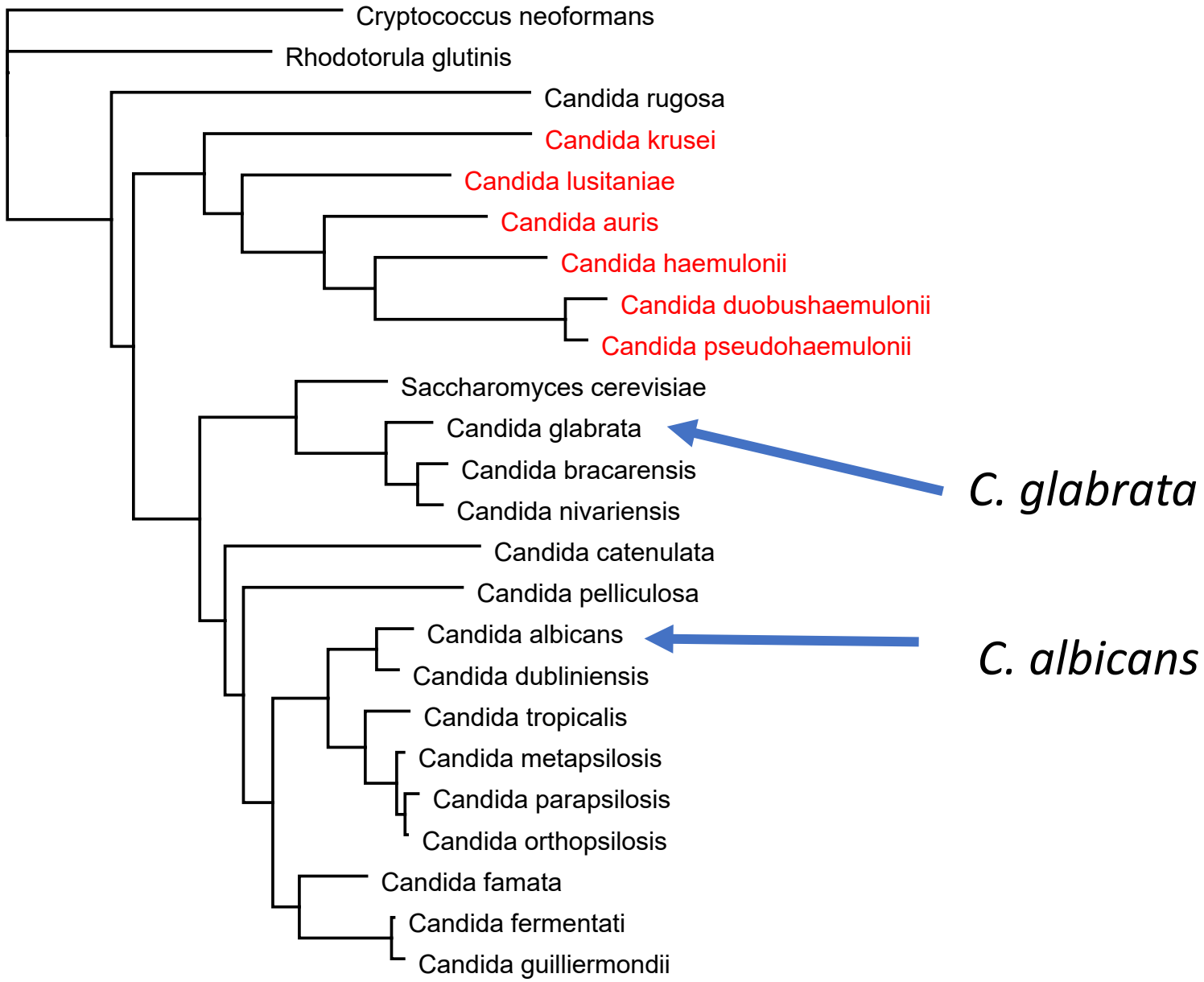


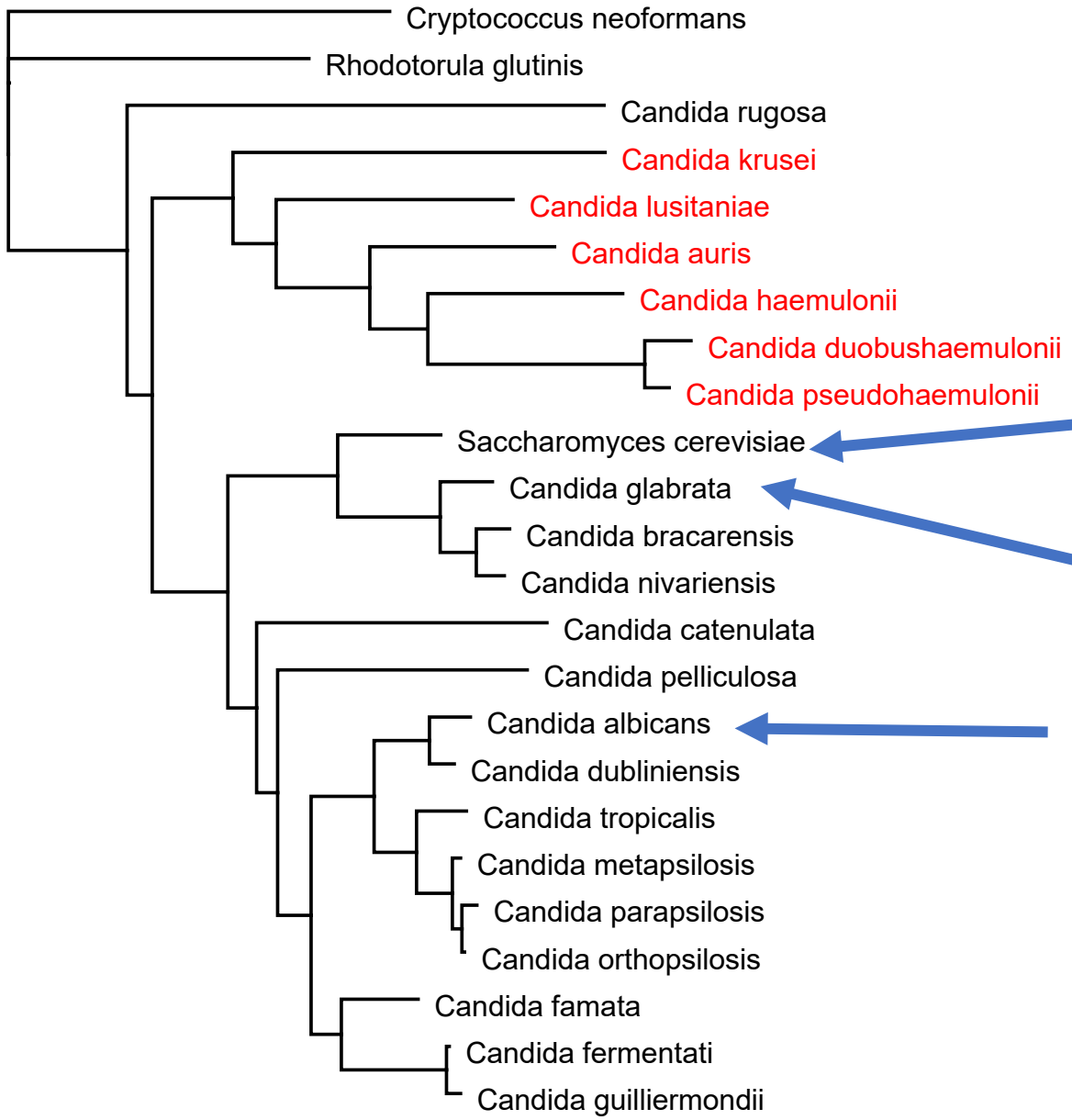
Chow et al, Multiple introductions and subsequent transmission of multidrug-resistant Candida auris in the USA: a molecular epidemiological survey; Lancet ID, Oct 2018

Not Like the Others



Closely related to other *Candida* species known for antifungal resistance


Cryptococcus neoformans
Rhodotorula glutinis
Candida rugosa
Candida krusei
Candida lusitaniae
Candida auris
Candida haemulonii
Candida duobushaemulonii
Candida pseudohaemulonii
Saccharomyces cerevisiae
Candida glabrata
Candida bracarensis
Candida nivariensis
Candida catenulata
Candida pelliculosa
Candida albicans
Candida dubliniensis
Candida tropicalis
Candida metapsilosis
Candida parapsilosis
Candida orthopsilosis
Candida famata
Candida fermentati
Candida guilliermondii
C. glabrata
C. albicans

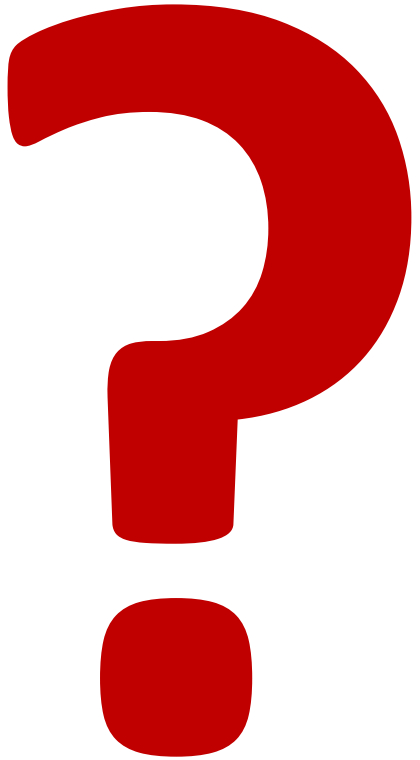


Saccharomyces

C. glabrata

C. albicans

Where did *C. auris* come from?



One hypothesis…

The New York Times

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Fungus Immune to Drugs Quietly Sweeps the Globe

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A New Public Health Threat

a new example of one of the world’s most intractable health threats: the rise of drug-resistant infections.

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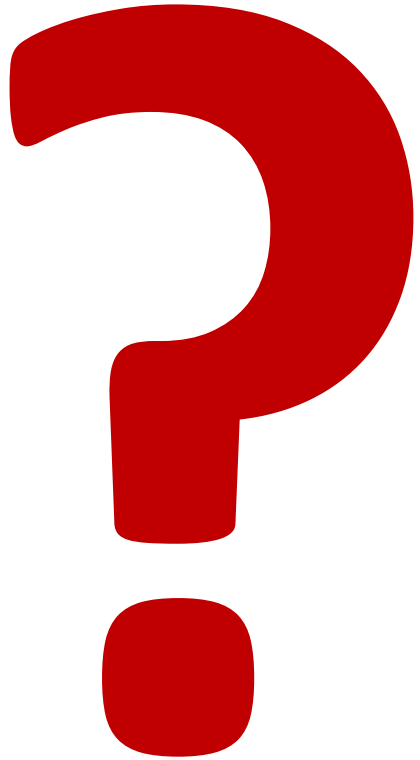
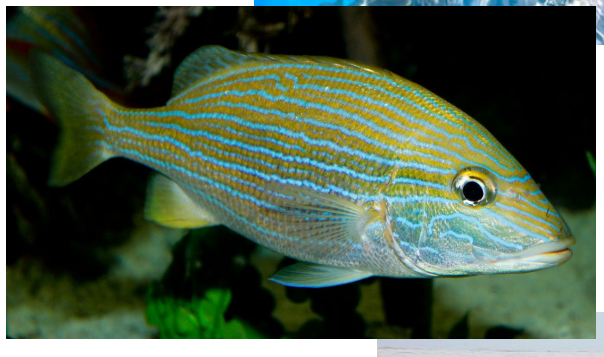
Where did *C. auris* come from?

- **It's not new to the world:** it's been here somewhere
- Its emergence **wasn't just better detection** (though that likely played a minor role)
- **Modern healthcare** clearly provided **fertile ground for spread**
- Probably **multiple spillover events** from the environment



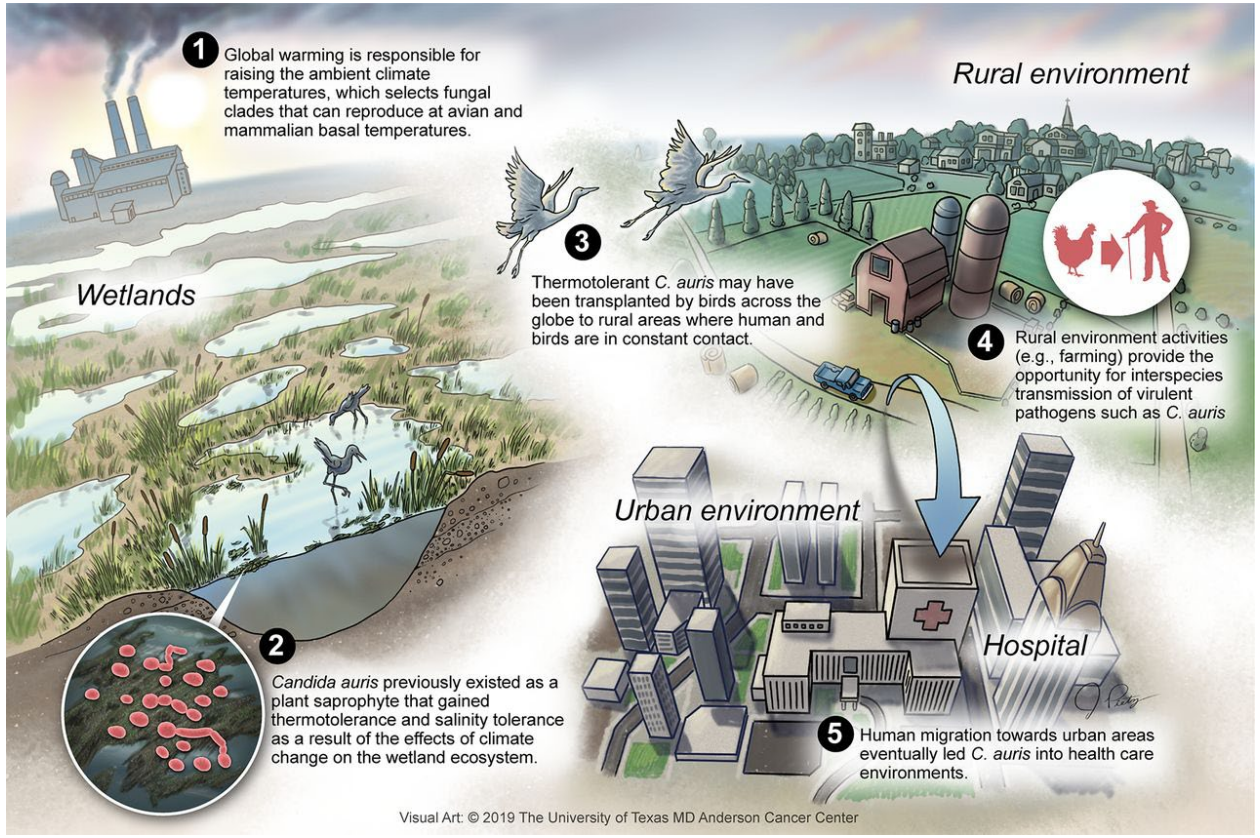
Where *C. auris* relatives have been found



Opinion/Hypothesis | Host-Microbe Biology

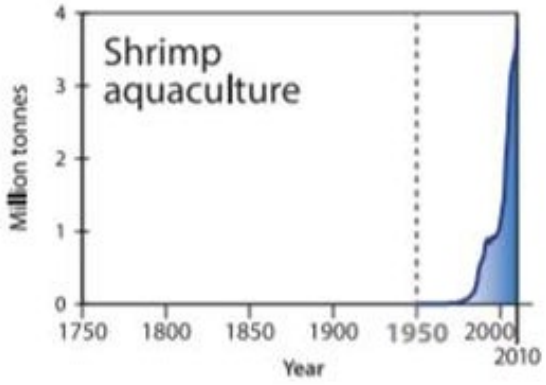
On the Emergence of *Candida auris*: Climate Change, Azoles, Swamps, and Birds

Arturo Casadevall, Dimitrios P. Kontoyiannis, Vincent Robert



Speculative hypotheses include…

- Role of climate change
- Human intrusion into existing habitat (e.g., deforestation)
- Human activities amplifying reservoir (e.g., shrimp aquaculture, with antibiotic and fungal probiotic use)
- Role of environmental fungicides/antifungals
- Changes to human host (e.g., microbiome)



The trajectory of the Anthropocene: The Great Acceleration - Will Steffen, Wendy Broadgate, Lisa Deutsch, Owen Gaffney, Cornelia Ludwig, 2015 (sagepub.com)

Recently found in the wild

NEWS HEALTH & MEDICINE

ScienceNews
INDEPENDENT JOURNALISM SINCE 1921

A deadly fungus behind hospital outbreaks was found in nature for the first time

The discovery could spur search expeditions for the yeast in more places

Researchers found the yeast *Candida auris* in the Andaman Islands (shown) in the Indian Ocean, the first time the fungus has been isolated in the environment.

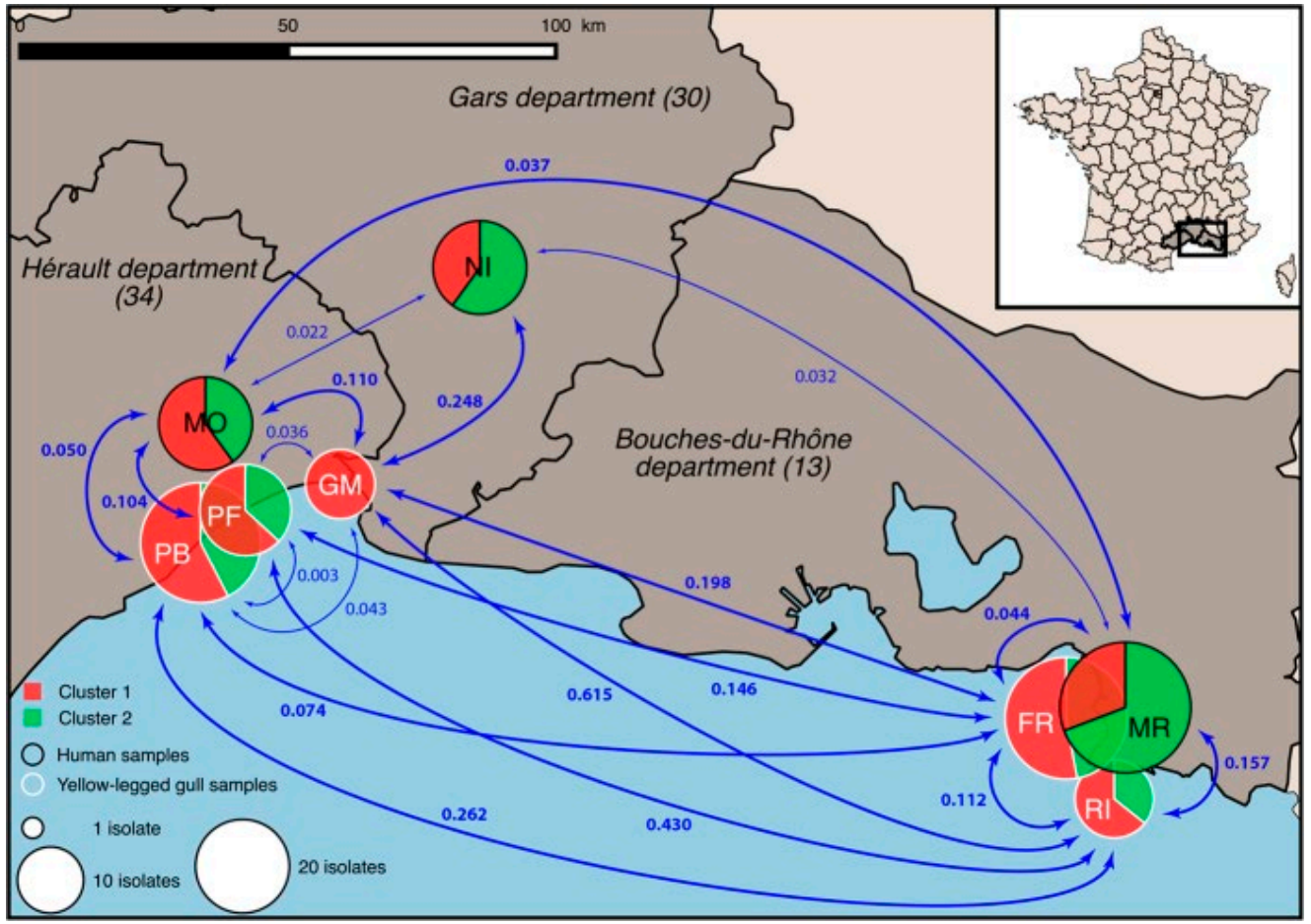
DUSHYANT THAKUR PHOTOGRAPHY/MOMENT/GETTY IMAGES

Increasing environmental links for common *Candida* species

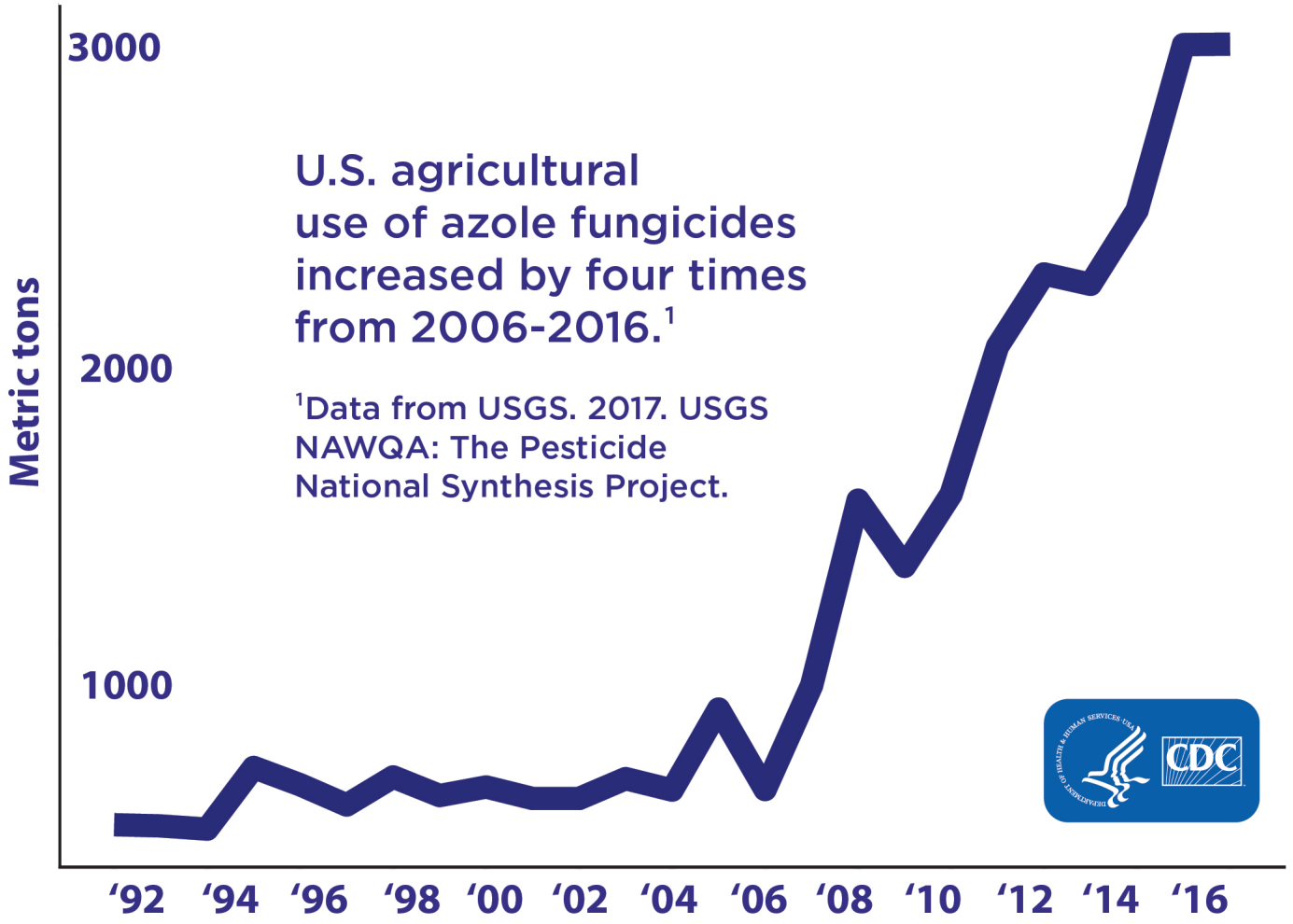
Does Candida grow on trees?

An opportunistic human pathogen makes itself at home on old oaks.

Opportunistic fungal pathogen *Candida glabrata* circulates between humans and yellow-legged gulls



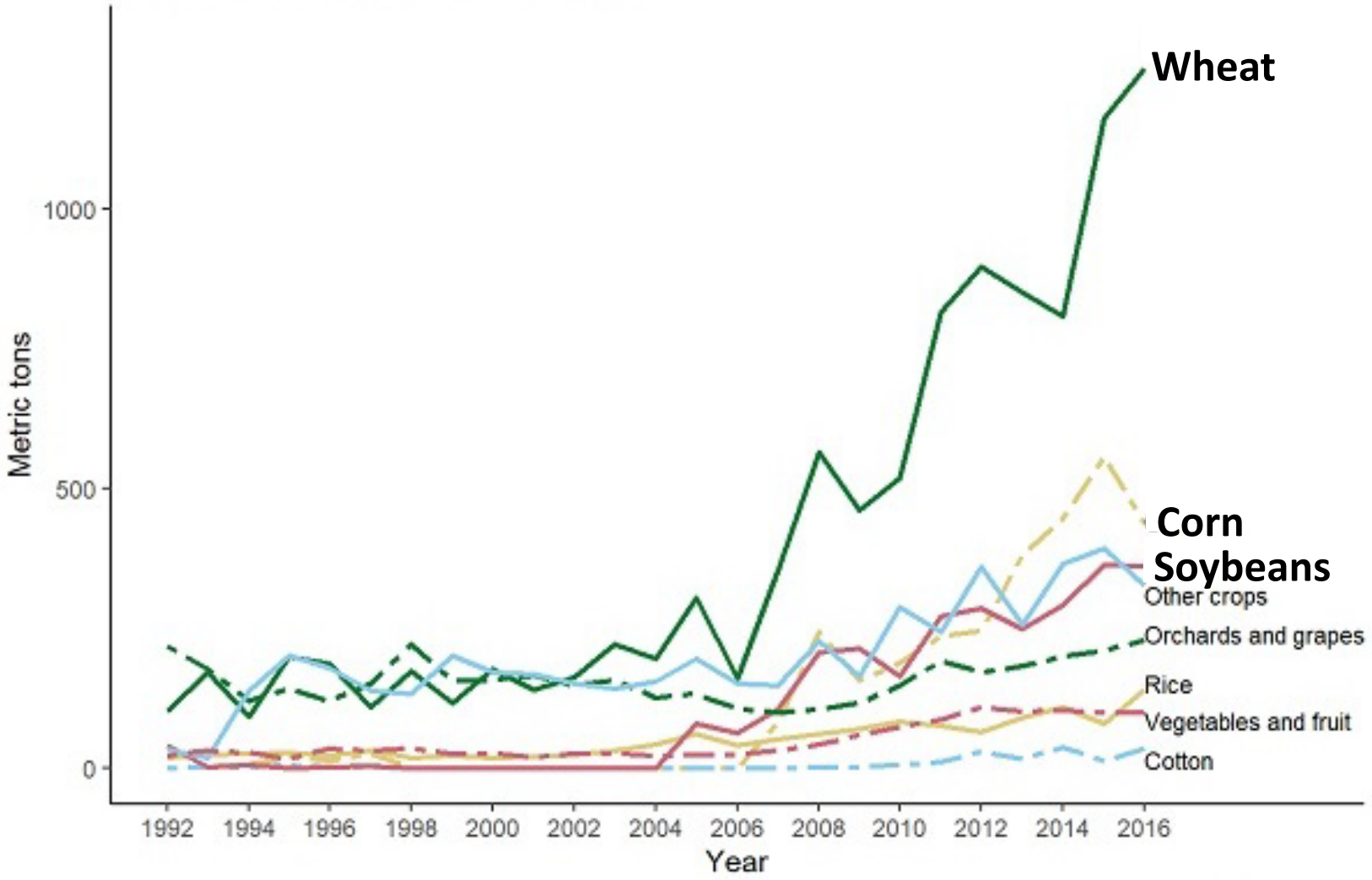
Over four-fold increase in agricultural azole fungicide use in United States



CS323341-A

Toda M, et al. Enviro Health Persp. 2021

Azole fungicide increases largely driven by wheat, corn, soybeans



Possible links between *Candida* resistance and agricultural fungicides?

Exposure of *Candida parapsilosis* complex to agricultural azoles: An overview of the role of environmental determinants for the development of resistance

Exposure of Candida parapsilosis complex to agricultural azoles: An overview of the role of environmental determinants for the development of resistance - ScienceDirect

Candida key points

- **Common causes** of human infection, including **severe infection**
- Limited treatment options, **increasingly compromised by resistance**
- **Environment** appears to play much stronger role than once thought

Thank you, with acknowledgments to the many people around the world and at CDC who work to prevent and treat *Candida* infections

Email: brjackson1@cdc.gov

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