



Candida auris, an Emerging Pathogen of Concern

Clinical Laboratory Advisory Council Annual Conference

Tuesday, November 12, 2019



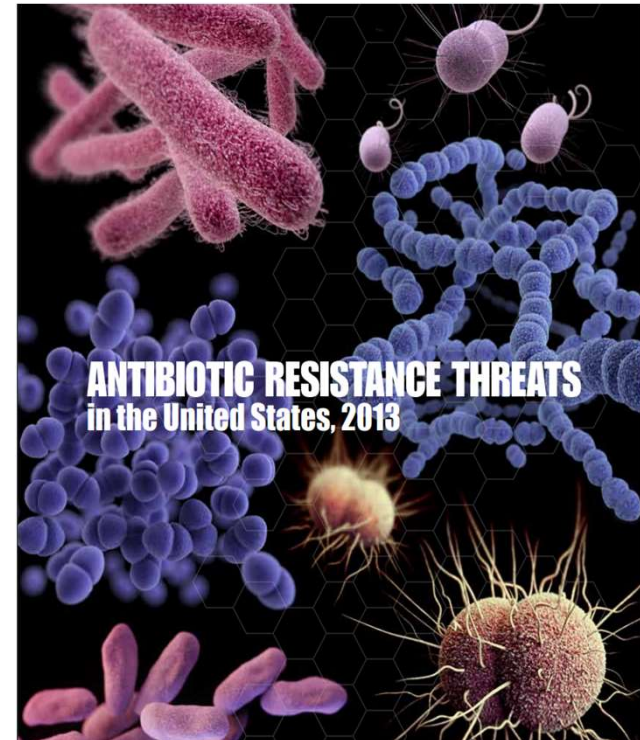
Outline



- The Antibiotic Resistance Lab Network (AR Lab Network)
- *C. auris*, an Emerging Pathogen of Concern
- Understanding *C. auris* Containment

Why do we care?

- **First fungal pathogen categorized as a public health threat.**
 - Ability to colonize skin, leading to infections
 - Rapid spread and ability to cause outbreaks
 - Severe disease with high mortality
 - Ability to persist on fomites
 - Difficult to identify with traditional lab testing
 - Elevated antifungal resistance





The New York Times

What You Need to Know About Candida Auris

C. auris is a mysterious and dangerous fungal infection that is among a growing number of germs that have evolved defenses against common medicines. Here are some basic facts about it.

Candida Auris: Here's why it's a superbug and what that means

Candida Auris: The Fungus Nobody Wants to Talk About

Live TV U.S. Edition

This drug-resistant fungus is spreading Scientists warn of new superbugs to come

serious global health threat: drug-resistant
now about Candida

How a Chicago Woman Fell Victim to Candida Auris, a Drug-Resistant Fungus

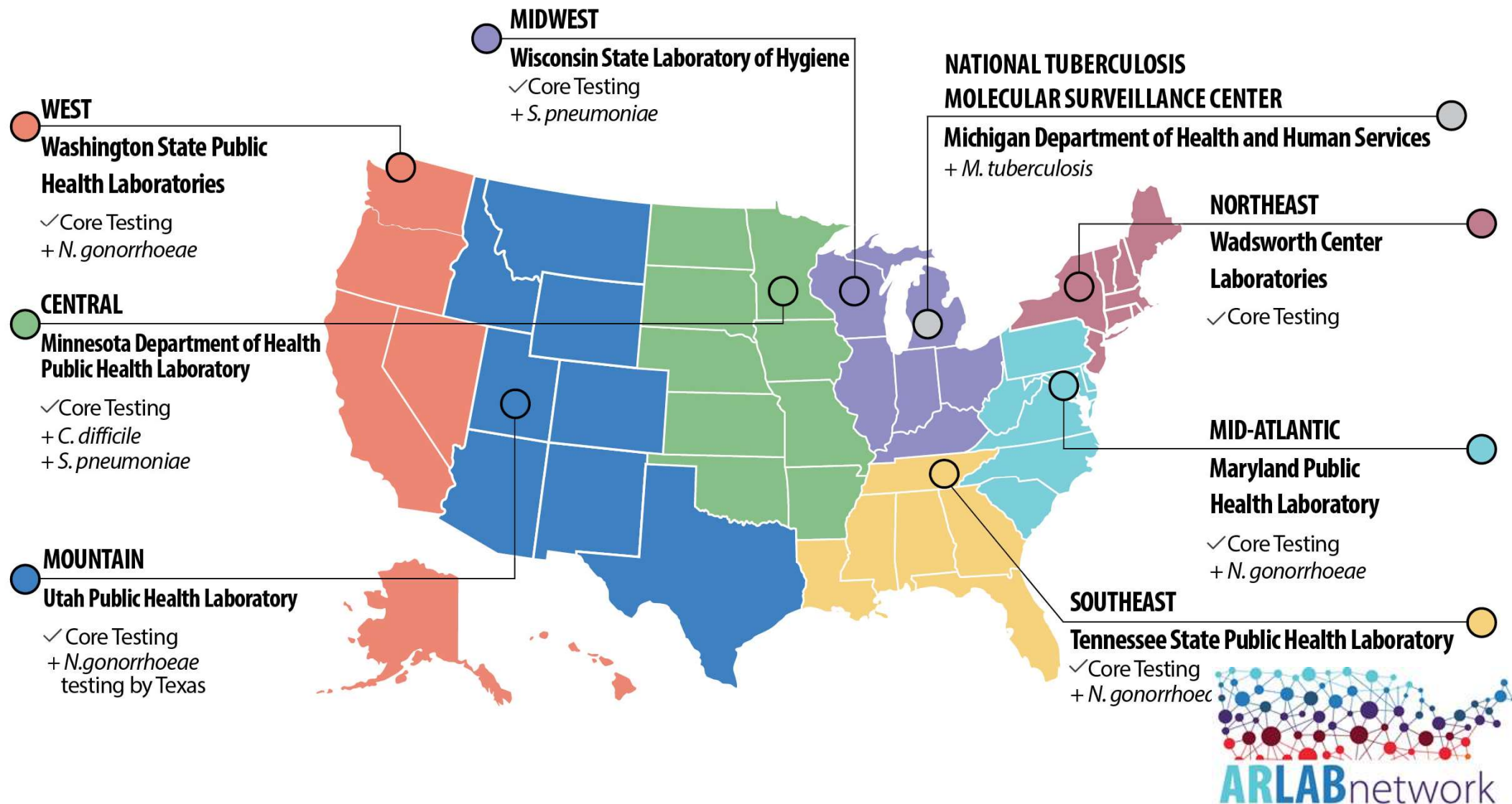
The mysterious infection has appeared at hospitals around the world. Some institutions or families have discussed their



Schumer Calls On CDC To Declare Emergency Over Superbug Fungus Spreading In N.Y.

The Antibiotic Resistance Lab Network





AR Lab Network Test Menu

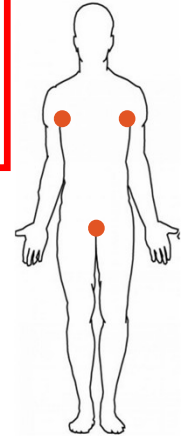


Isolate Submission

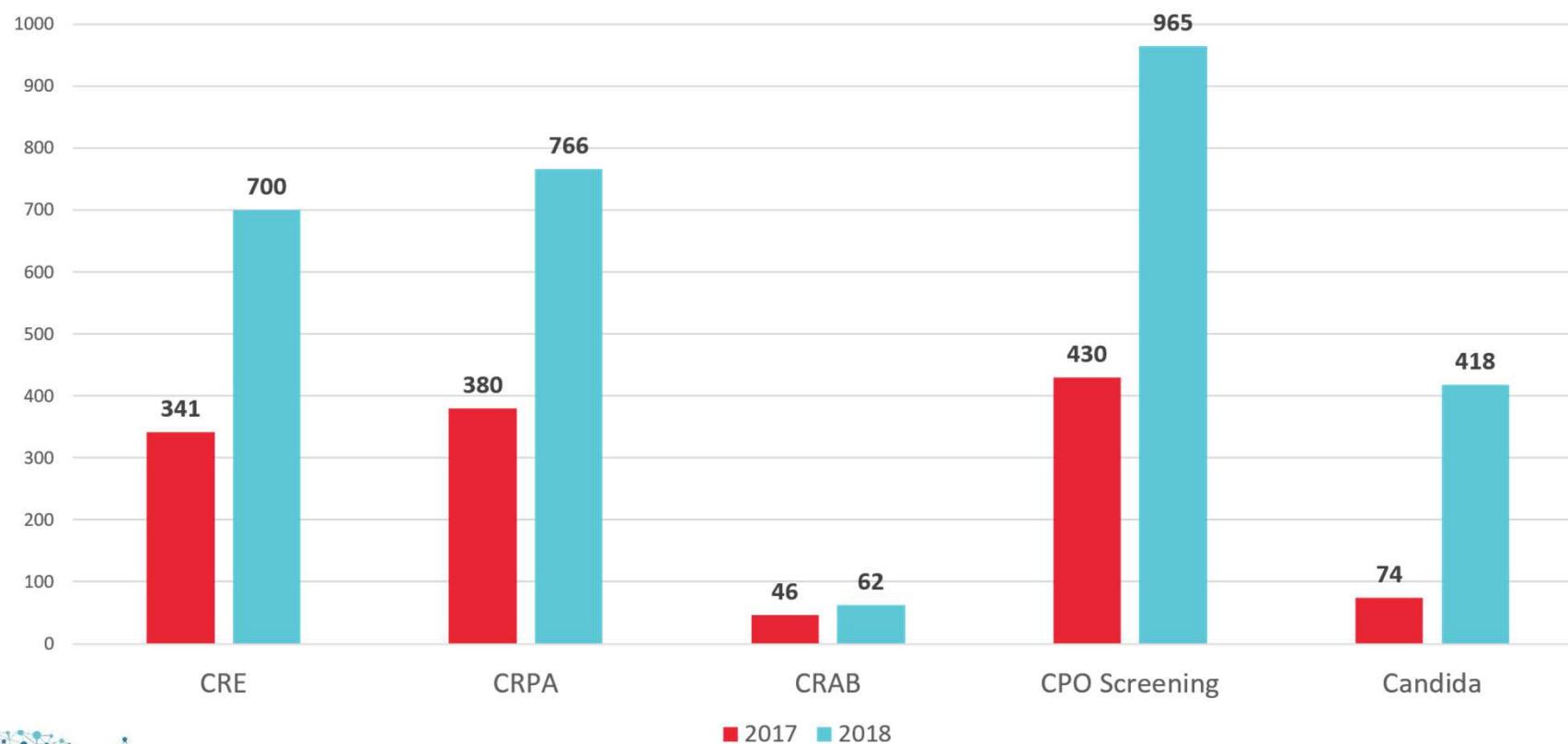
- Carbapenem-resistant *Enterobacteriaceae* (**CRE**) testing
- Carbapenem-resistant *Pseudomonas aeruginosa* (**CRPA**) testing
- Carbapenem-resistant *Acinetobacter baumannii* (**CRAB**) testing
- ***Candida (non-albicans)* species identification and susceptibility testing**

Colonization Screening

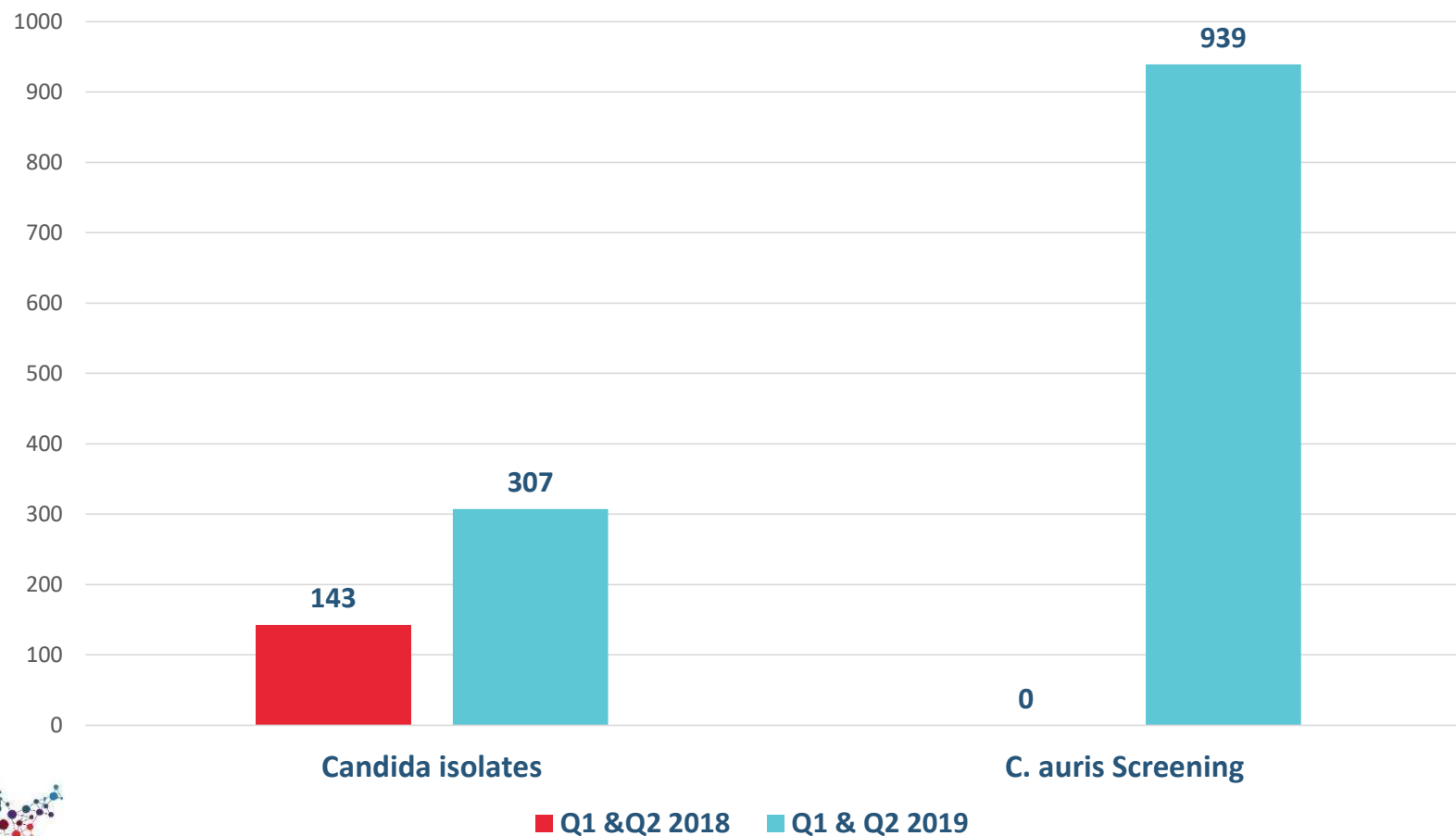
- Carbapenemase-producing organism (**CPO**) colonization screening
- ***Candida auris* colonization screening**



{STATE} Submission Data, 2017 & 2018



{STATE} Submissions, Q1 & Q2, 2018 and 2019



{State} *Candida* Submissions, 2018



“Top 10” *Candida* species identified, 2018
n=418

Rank	Species	Total	% Total
1	<i>Candida glabrata</i>	223	53.3%
2	<i>Candida parapsilosis</i>	57	13.6%
3	<i>Candida lusitaniae</i>	34	8.1%
4	<i>Candida tropicalis</i>	20	4.8%
5	<i>Candida kefyr</i>	14	3.3%
6	<i>Candida krusei</i>	10	2.4%
6	<i>Candida dubliniensis</i>	10	2.4%
8	<i>Candida guilliermondii</i>	9	2.2%
9	<i>Candida metapsilosis</i>	6	1.4%
10	<i>Candida haemulonii</i>	5	1.2%
10	<i>Candida duobushaemulonii</i>	5	1.2%
10	<i>Candida albicans</i>	5	1.2%

{STATE} *Candida* Submissions, 2018



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Top 5 Causes of Infection

Rank	Species
1	<i>Candida albicans</i>
2	<i>Candida glabrata</i>
3	<i>Candida parapsilosis</i>
4	<i>Candida tropicalis</i>
5	<i>Candida krusei</i>

{STATE} *Candida* Submissions, 2018



State Map of Sentinel Labs

- 280 *Candida* isolates submitted in 2018
- 94.6% of isolates came from sentinel labs
- No *C. auris* detected

C. auris, an Emerging Pathogen of Concern



The Discovery of *C. auris*



- 2009
- Tokyo, Japan
- 70-year-old woman, seeking inpatient care
- A novel yeast is isolated from her ear canal
- Isolate exhibited unusual growth characteristics
- Phylogenetic tree was constructed and the mysterious strain clustered in the Metschnikowaeaceae clade
 - Similar to *C. haemulonii*, *C. pseudohaemulonii*
- The proposed name of this new species:

Candida auris

Retrospective Analysis of *Candida* Isolates



- **2 misidentified *Candida* isolates discovered**
 - 1996- South Korean patient with fungemia
 - 2008- Pakistani isolate
- No *C. auris* detected before 2009 in a review of SENTRY and ARTEMIS isolates
 - >30,000 isolates from 4 continents, 1996-2015
- No *C. auris* detected in a review of EIP *Candida* surveillance isolates
 - 7,000 isolates, 2008-2016

Where did *C. auris* come from?



- **Theory #1:** *C. auris* was circulating unrecognized, with historical separation from an ancestral strain
 - Would be a possible explanation for the independent clonal expansion
 - Lack of retrospective identification is contradictory
- **Theory #2:** Development of a common environmental niche
 - Use of broad-spectrum antifungals continues to increase
 - Immunosuppressed, growing intensive care population
 - Fungicides in agriculture
 - Climate change



C. auris Growth Characteristics

- Pink to beige colonies on CHROMagar *Candida* medium
- Grows well at 42°C
 - An important characteristic that helps differentiate *C. auris* from *C. haemulonii*
- High salt tolerance
- Microscopic morphology: oval or elongated
 - hyphal or pseudohyphal forms are not observed



Mixed culture of *Candida glabrata* (purple), *Candida tropicalis* (navy blue), and *Candida auris* (white, circled in red) on CHROMagar Candida.



Candida auris on CHROMagar Candida, displaying multiple color morphs.



Potential Virulence Factors

- **Aggregation:** budding occurs, but daughter cells not released, resulting in large “clumps”
 - In animal models, aggregates seem to be a mode of immune evasion and persistence in tissues
- **Lytic enzymes**
 - Hydrolases are the largest group of enzymes found in *C. auris*
 - Production is strain dependent
- **Pathogenicity maintained at high temperatures**
- **Biofilm formation:** important for resistance and immune evasion
 - Variable biofilm production
 - Increased resistance
 - Persistence on indwelling medical devices and fomites

Immune Response to *C. auris*

- Neutrophils kill fungi through phagocytosis and neutrophil extracellular trap (NET) formation
- However, for *C. auris*, phagocytosis or NET release fails
- This may in part account for high mortality rates

Candida auris
Candida albicans
Neutrophils

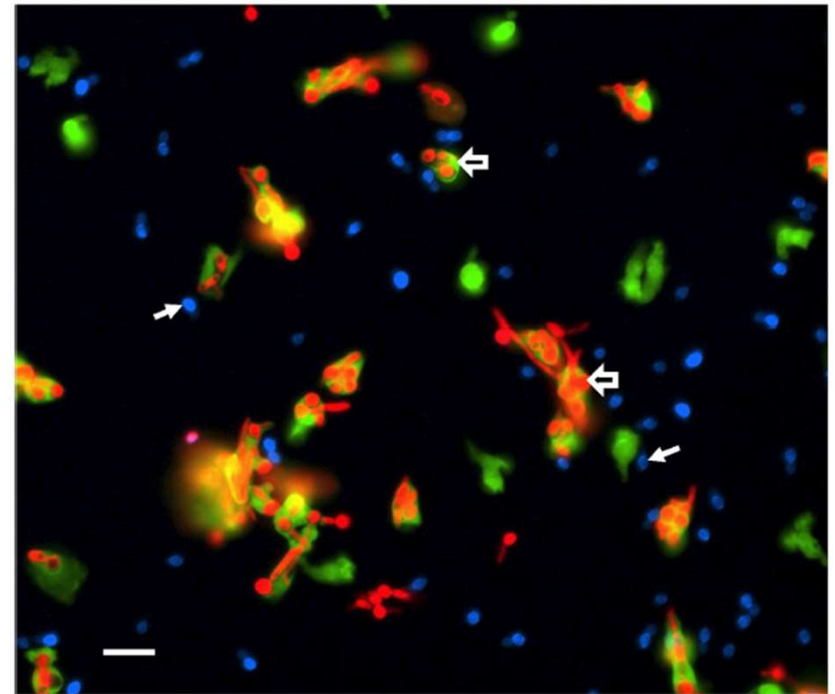


Fig 1. Human neutrophils fail to engage *Candida auris*. Calcein AM-labeled human neutrophils (green) were cocultured with red fluorescent protein-tagged *C. albicans* (red) and calcofluor white-stained *C. auris* (blue) for 30 min. Neutrophils preferentially engaged *C. albicans*, ignoring *C. auris*. Open arrows point to neutrophils phagocytosing *C. albicans*. Closed arrows show *C. auris* cells. Few neutrophils engage *C. auris* in the presence or absence of *C. albicans*. Measurement bar represents 10 μm.

<https://doi.org/10.1371/journal.ppat.1007638.g001>

Resistance Concerns



- Resistance is a major problem because limited antifungal drugs are available
- No antifungal clinical breakpoints for *C. auris*



Resistance: *C. auris*

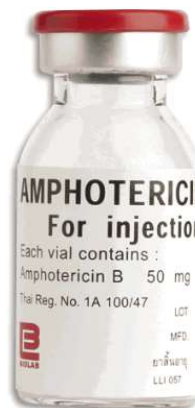
1



88%

Azoles

2



34%

Polyenes

3



2%

Echinocandins

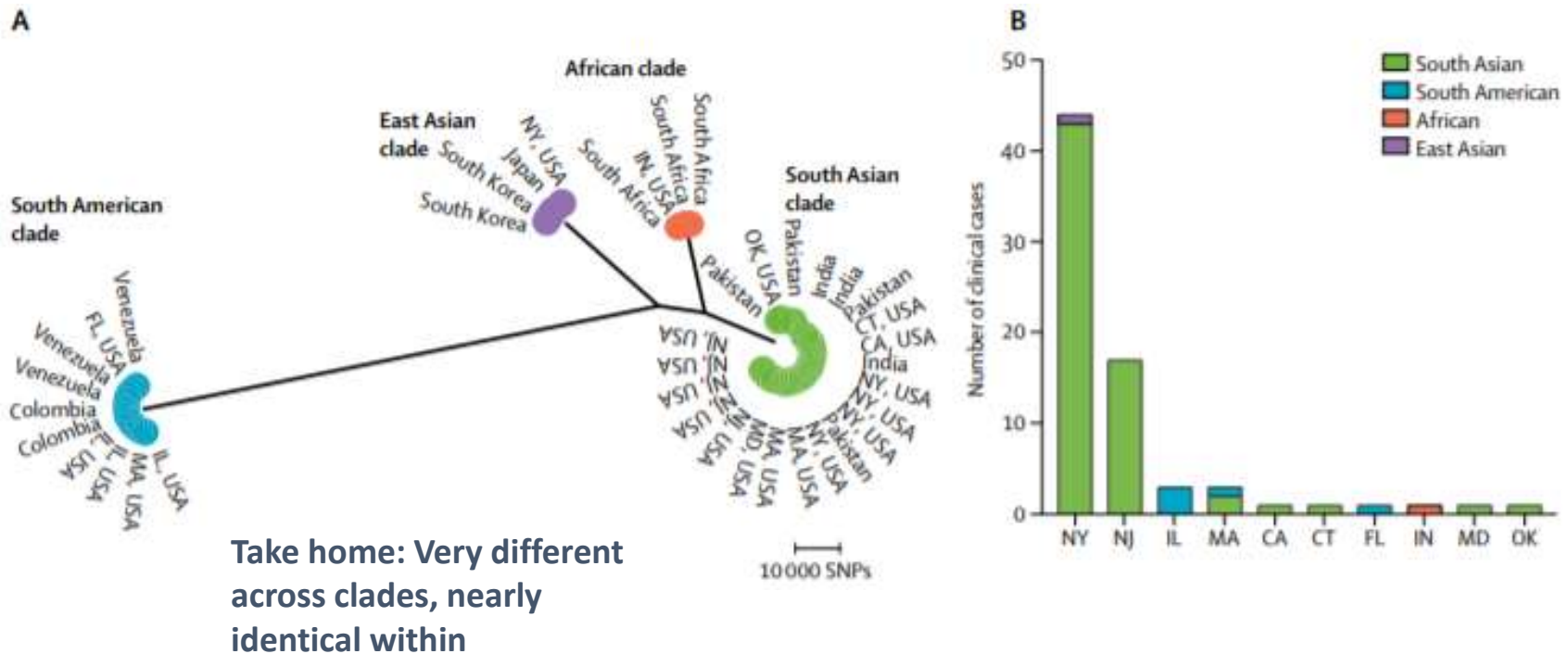
- 33% multidrug-resistant
- **3 pan-resistant cases found in 2019**

Clades



- Four* clades: South Asian, South African, South American and East Asian
 - Widespread variation between clades (over 10,000 SNP difference)
 - Minimal variation within clades (often differing by less than 100 SNPs)
- Simultaneous detection in different geographical locations
- Display distinct mechanisms of antifungal resistance

The Four* Clades of *C. auris*



Is There a Fifth Clade of *C. auris*?



Potential Fifth Clade of *Candida auris*, Iran, 2018

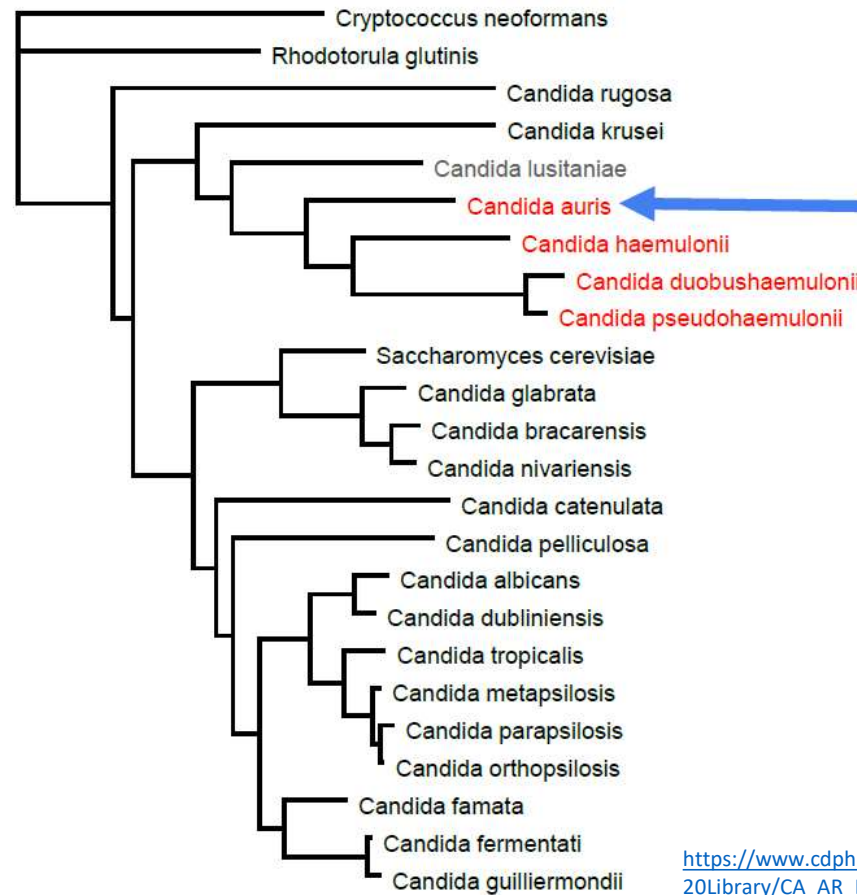
Nancy A. Chow, Theun de Groot, Hamid Badali, Mahdi Abastabar, Tom M. Chiller, Jacques F. Meis

Author affiliations: Centers for Disease Control and Prevention, Atlanta, Georgia, USA (N.A. Chow, T.M. Chiller); Canisius Wilhelmina Hospital, Nijmegen, the Netherlands (T. de Groot, J.F. Meis); Mazandaran University of Medical Sciences, Sari, Iran (H. Badali, M. Abastabar)

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6711235/pdf/19-0686.pdf>

- Isolated from the ear of a 14-year-old girl (Iran)
- Isolate was genetically distinct from the 4 existing clades
 - >200,000 SNPs
 - Most closely related to the East Asian clade

Phylogeny



https://www.cdph.ca.gov/Programs/CHCQ/HAI/CDPH%20Document%20Library/CA_AR_LabNetwork_C.auris062717.pdf

Identification Issues



Identification Method	Organism <i>C. auris</i> can be misidentified as
Vitek 2 YST	<i>Candida haemulonii</i> <i>Candida duobushaemulonii</i>
API 20C	<i>Rhodotorula glutinis</i> (characteristic red color not present) <i>Candida sake</i>
BD Phoenix yeast identification system	<i>Candida haemulonii</i> <i>Candida catenulata</i>
MicroScan	<i>Candida famata</i> <i>Candida guilliermondii</i> * <i>Candida lusitanae</i> * <i>Candida parapsilosis</i> *
RapID Yeast Plus	<i>Candida parapsilosis</i> *



Identification with MALDI-TOF-MS

- Matrix Assisted Laser Desorption/Ionization Time of Flight Mass Spectroscopy (**MALDI-TOF-MS**)
- Compares spectra acquired for a sample to a database of spectra for known isolates
- Comparison is scored on a log scale (between 0-3)

Range	Description	Symbols	Color
2.300 ... 3.000	highly probable species identification	(+++)	green
2.000 ... 2.299	secure genus identification, probable species identification	(++)	green
1.700 ... 1.999	probable genus identification	(+)	yellow
0.000 ... 1.699	not reliable identification	(-)	red

<https://slideplayer.com/slide/10455908/>

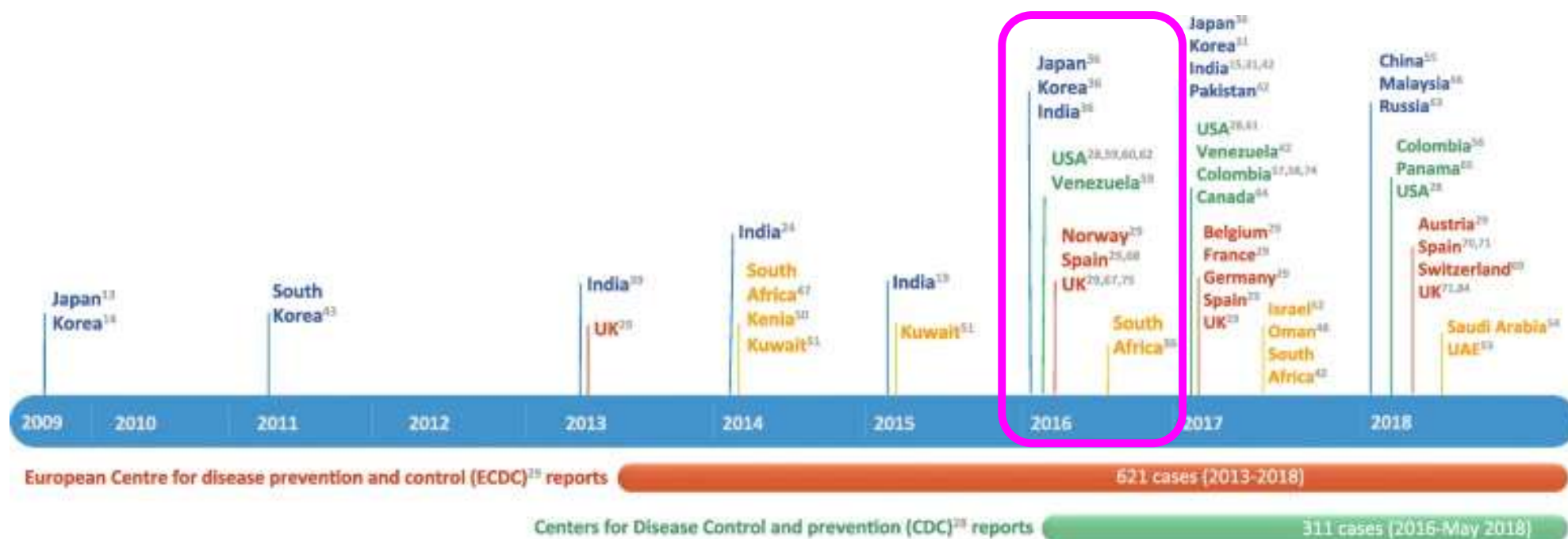
Limitations Associated with MALDI-TOF Identification



- Commercial databases from different MALDI-TOF manufacturers differ
- Expensive!



Timeline of Emergence



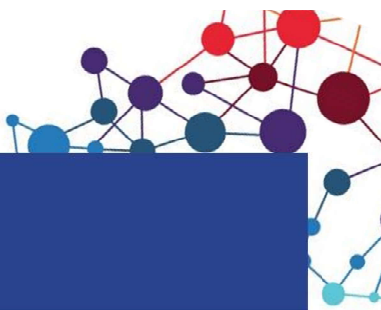


Clinical Alert to U.S. Healthcare Facilities – June 2016

This clinical alert has been updated. Please read the [September 2017 *C. auris* Clinical Update](#) with important information from investigations of U.S. cases of *C. auris* for clinicians, laboratorians, and public health officials.

Global Emergence of Invasive Infections Caused by the Multidrug-Resistant Yeast *Candida auris*

Summary: The Centers for Disease Control and Prevention (CDC) has received reports from international healthcare facilities that *Candida auris*, an emerging multidrug-resistant (MDR) yeast, is causing invasive healthcare-associated infections with high mortality. Some strains of *C. auris* have elevated minimum inhibitory concentrations (MICs) to the three major classes of antifungals, severely limiting treatment options. *C. auris* requires specialized methods for identification and could be misidentified as another yeast when relying on traditional biochemical methods. CDC is aware of one isolate of *C. auris* that was detected in the United States in 2013 as part of ongoing surveillance. Experience outside the United States suggests that *C. auris* has high potential to cause outbreaks in healthcare facilities. Given the occurrence of *C. auris* in nine countries on four continents since 2009, CDC is alerting U.S. healthcare facilities to be on the lookout for *C. auris* in patients.



Morbidity and Mortality Weekly Report (MMWR)

Investigation of the First Seven Reported Cases of *Candida auris*, a Globally Emerging Invasive, Multidrug-Resistant Fungus — United States, May 2013–August 2016

Weekly / November 11, 2016 / 65(44);1234–1237

- From June 2016– August 31, 2016, 7 cases were detected
 - 6/7 detected through retrospective review



https://www.cdc.gov/mmwr/volumes/65/wr/mm6544e1.htm#T1_down

Case Characteristics



TABLE. Characteristics of the first seven cases of *Candida auris* identified in the United States—May 2013–August 2016

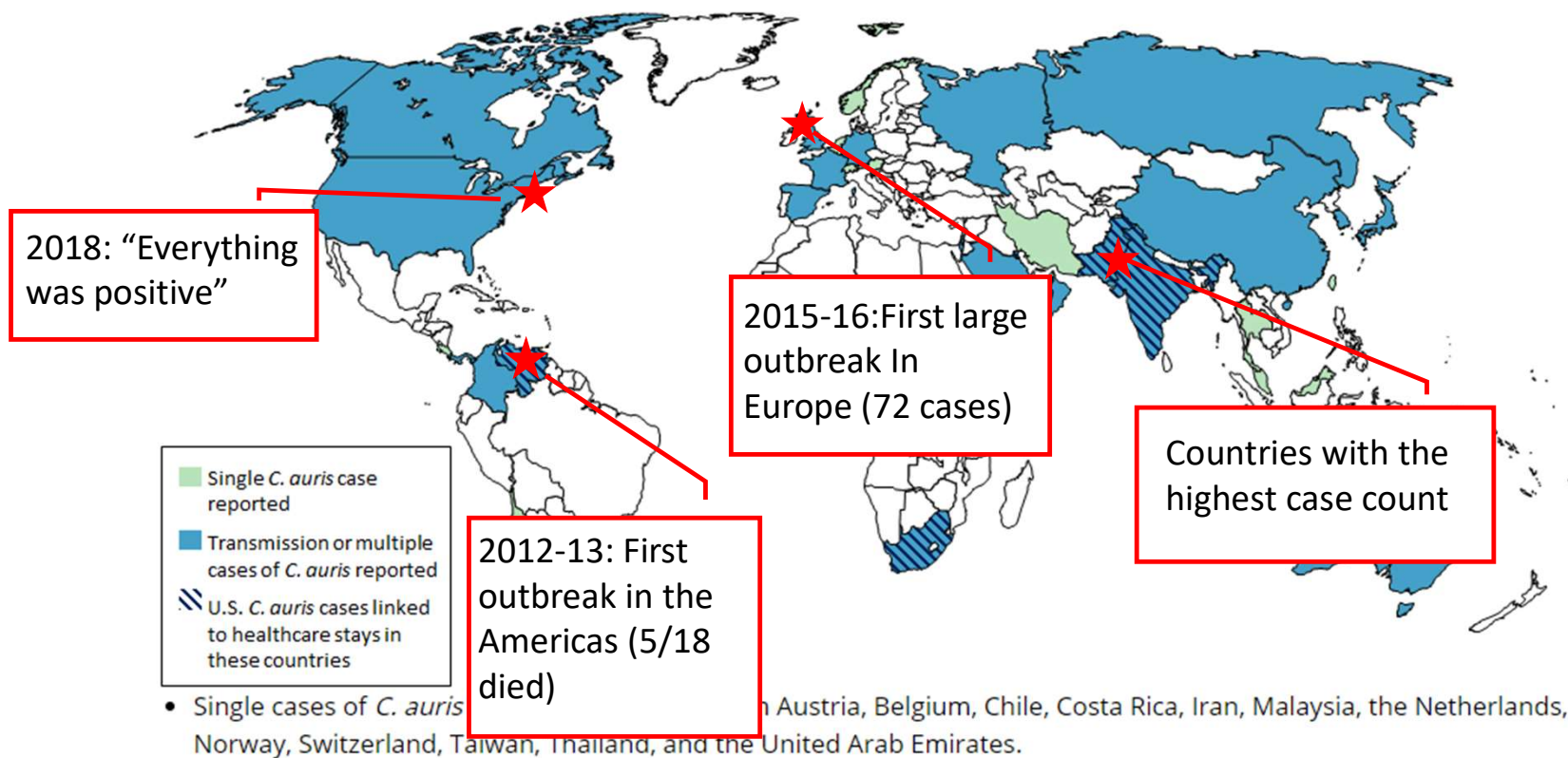
Patient	Isolation month/ year	State	Site of <i>C. auris</i> isolation	Underlying medical condition(s)	Outcome*
1	May 2013	New York	Blood	Respiratory failure requiring high-dose corticosteroids	Died
2	July 2015	New Jersey	Blood	Brain tumor and recent villous adenoma resection	Died
3	April 2016	Maryland	Blood	Hematologic malignancy and bone marrow transplant	Died
4	April 2016	New York	Blood	Hematologic malignancy	Died
5	May 2016	Illinois	Blood	Short gut syndrome requiring total parenteral nutrition and high-dose corticosteroid use	Survived
6	July 2016	Illinois	Urine	Paraplegia with long-term, indwelling Foley catheter	Survived
7	August 2016	New York	Ear	Severe peripheral vascular disease and skull base osteomyelitis	Survived

* Mortality was not necessarily attributable to *C. auris* infection.

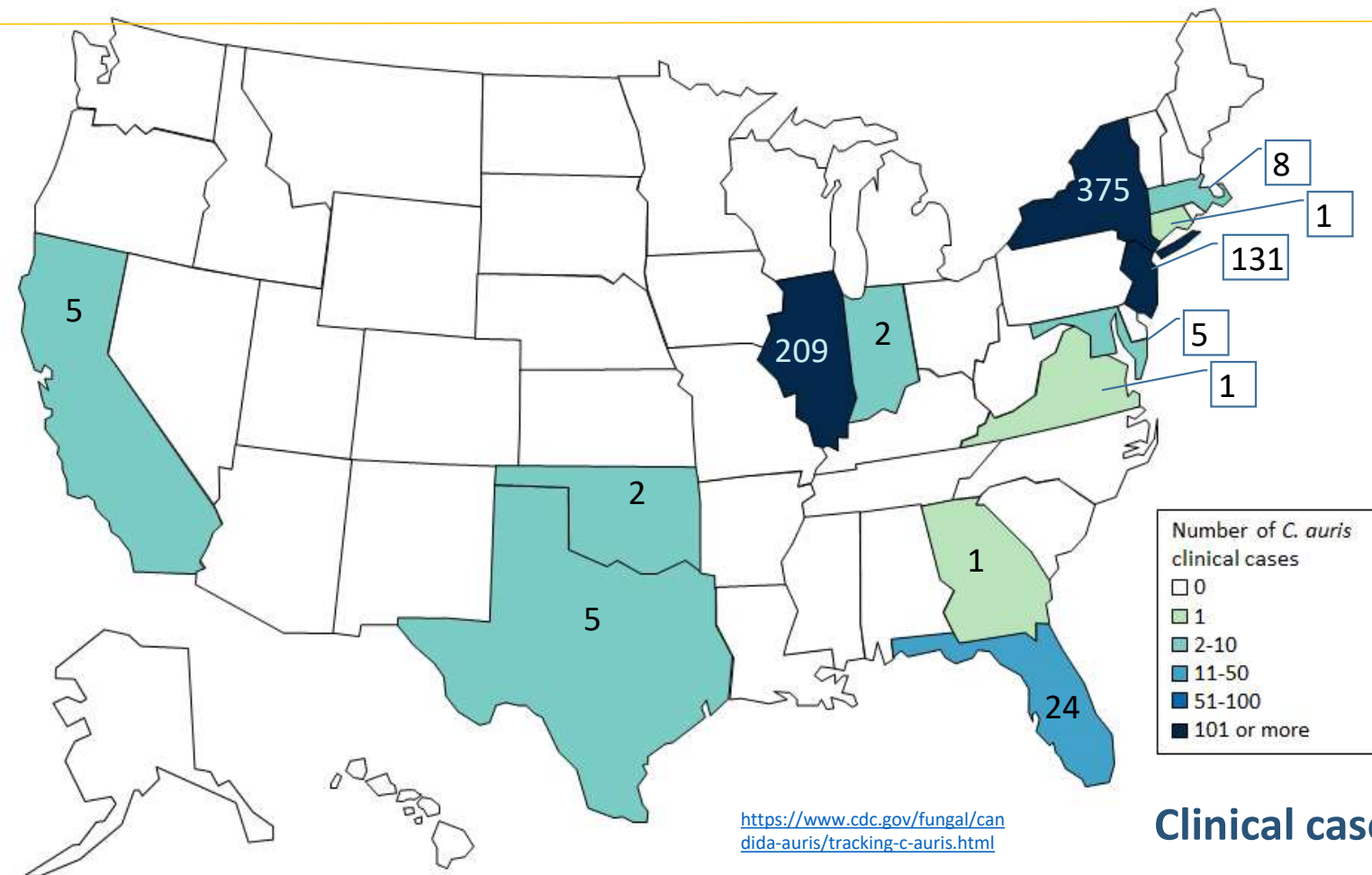


https://www.cdc.gov/mmwr/volumes/65/wr/mm6544e1.htm#T1_down

Countries from which *Candida auris* cases have been reported, as of May 31, 2019

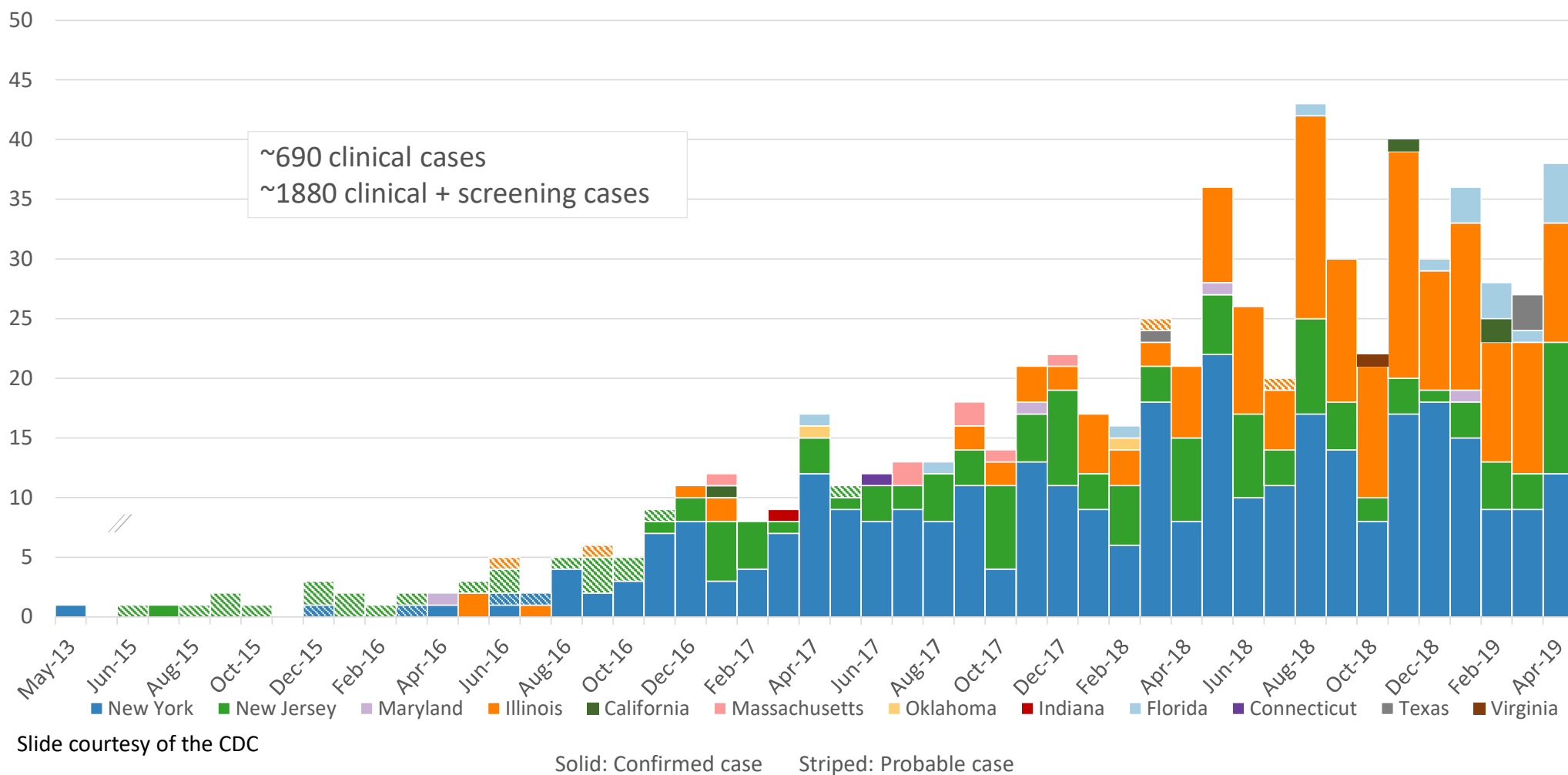


U.S. Map: Clinical cases of *Candida auris* reported by U.S. states, as of July 31, 2019



Clinical cases= 789

C. auris clinical cases reported by state of collection— United States, 2013–April 2019

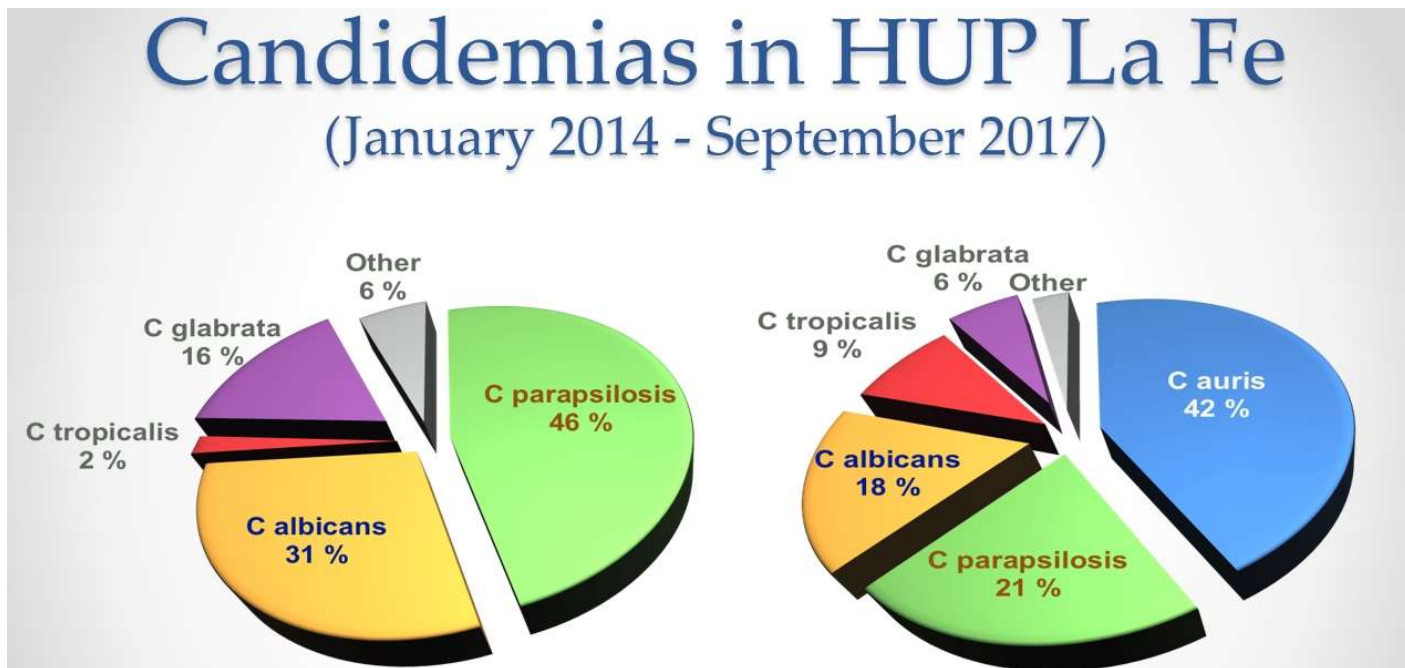


Slide courtesy of the CDC

Solid: Confirmed case Striped: Probable case

Changing Epidemiology of Candidemia

- *C. auris* cases are additive, increasing overall Candidemia rate
- Shift from *Candida albicans* to non-*albicans* species



<https://www.eccmidlive.org/#resources/how-should-we-manage-the-c-auris-outbreak>

Understanding *C. auris* Containment





Case Definitions

Confirmed Clinical Case

- Person with confirmatory laboratory evidence from a clinical specimen collected for the purpose of diagnosing or treating disease in the normal course of care.
 - This includes specimens from sites reflecting invasive or non-invasive infection

Confirmed Colonized

- Person with confirmatory laboratory evidence from a swab collected for the purpose of screening for *C. auris* colonization regardless of site swabbed.
 - Typical colonization/screening specimen sites are skin (e.g., axilla, groin), nares, rectum, or other external body sites. Swabs from wound or draining ear are considered clinical.

C. auris Reporting



- *C. auris* is nationally notifiable (2019)
 - Clinical cases, not colonization
 - Reporting based on state of residence
- Will be added to the Washington State List of Notifiable Conditions with WAC update





Risk factors

- Contact with patients or environments known to harbor *C.auris*
- Healthcare in areas with ongoing *C. auris* transmission
- Critically ill patients
 - Care in high acuity facilities
 - Especially vSNFs
 - Indwelling medical devices
 - Central venous catheters (CVCs), urethral catheters, breathing tubes , feed tubes, etc.
 - Broad-spectrum antimicrobial treatment/prophylaxis

**Targets
the most
vulnerable
patients**

Transmission



- Efficient person-to-person transmission
 - Asymptomatically colonized patients can only be detected through screening
 - Hands of healthcare workers
 - Can spread rapidly in healthcare facilities
- Persist on the surfaces of hospital rooms and medical devices
 - >4 weeks on plastic



Clinical Symptoms

- May be difficult to detect because of patient comorbidities
- Symptoms vary based on infection type
 - 75% of US cases have been bloodstream
- **Clinically indistinguishable from infection with other *Candida* species**
 - **Lab testing is required to confirm infection**





Site of Infection

TABLE 3 *Candida auris* infection cases by disease type reported in the literature

Type of disease or location of Isolation ^b	No. of cases (reference[s])
Candidemia	291 (3–5, 7, 8, 10, 12, 14–16, 26, 27, 57, 58, 70, 71)
Central venous catheter tip	2 (70)
CNS	1 (12)
ENT	21 ^a (1, 17, 58, 70, 72)
Respiratory tract	18 (26, 27, 36, 70)
Urogenital system	17 (12, 27, 56)
Abdominal	13 (12, 27, 70)
Skin and soft tissue, including surgical wounds	12 (3, 10, 27, 70)
Bone	2 (12, 70)

^aTwo associated with otomastoiditis and 19 from ear swabs of patients with otitis externa.

^bCNS, central nervous system; ENT, ear, nose, and throat.

Mortality

- 30-60% Mortality
- Varies significantly geographically
- Overall attributable mortality rate is unclear
 - Underlying illness or *C. auris* infection?



Prevention

- Rapid implementation of infection control procedures
 - **Hand Hygiene**
 - PPE for patient care
 - Proper environmental cleaning
 - Proper cleaning of shared equipment
 - Contact precautions when appropriate
 - All patient known to be infected or colonized should be isolated
 - Education and practice audits
- Early detection
- Appropriate colonization screening



Identifying the species of *Candida* from urine and other non-sterile body sites

- Yeast from urine usually tossed out because not considered an infection
- Long-term acute care hospital network decided to speciate *Candida* from urines from all patients
- Within 5 months, detected first case of *C. auris* in their region



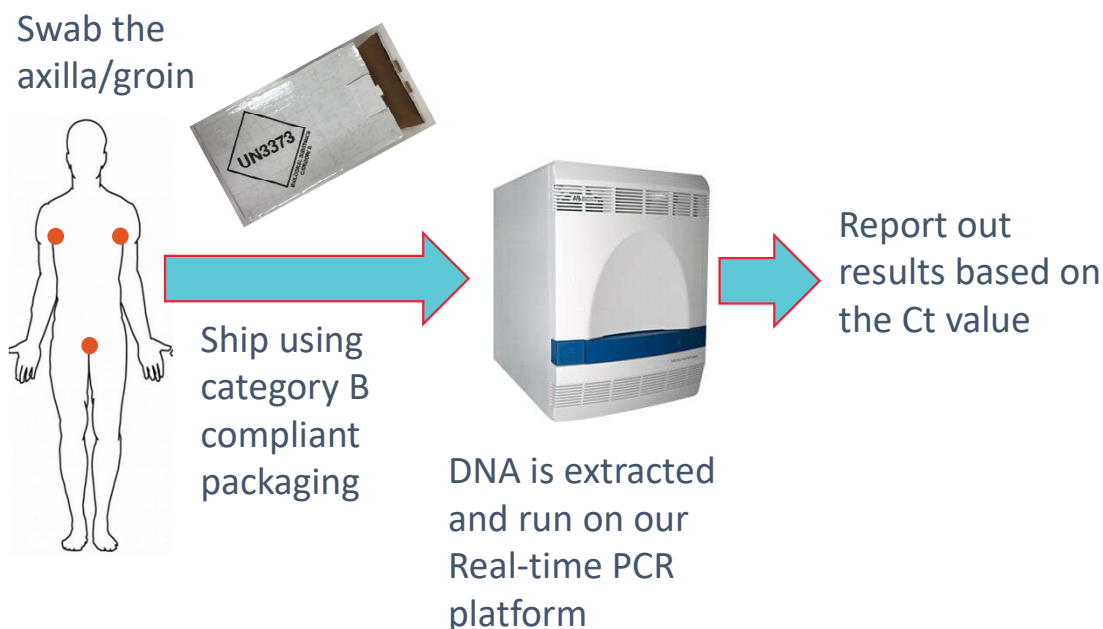
CDC Screening Recommendations



- **Close healthcare contacts** of patients with newly identified *C. auris* infection or colonization
- Patients who have had an **overnight stay in a healthcare facility outside the United States** in the previous one year, especially if in a country with documented *C. auris* cases.
 - Strongly consider screening when patients have inpatient healthcare exposures outside the US and have infection/colonization with carbapenemase-producing Gram-negative bacteria.



Screening Through the AR Lab Network

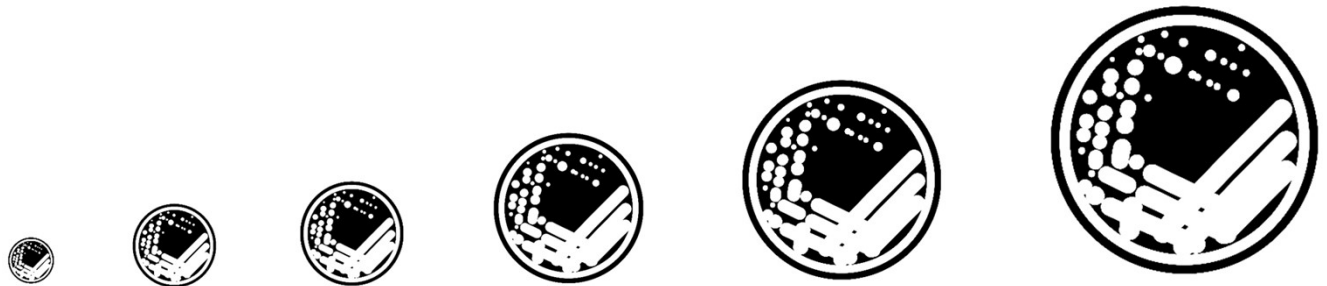


- All supplies provided at no cost
 - Collection kits
 - Shipping material
- PCR results in less than one week

Important Takeaways



- *C. auris* is difficult to identify with traditional lab tests
 - Identification is vital for containment!
- *C. auris* is a major threat to the most vulnerable patients
- *C. auris* case counts are increasing and it is spreading
- Rapid implementation of infection control practices is vital



Thank you for your attention!

Questions?

