MMTN
MEDICAL MYCOLOGY
TRAINING NETWORK

Evolving fungal landscape in Asia

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ASIA FUNGAL WORKING GROUP an ISHAM working group

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The Evolving Fungal Landscape in Asia

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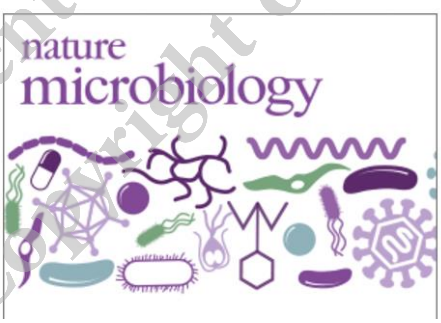
Outlines

- Stop neglecting fungi
- Emerging: *Candida auris*
- Unexpected: fungal infections after natural disasters
- One health: azole-resistant *Aspergillus fumigatus*
- Conclusion

PUBLISHED: 25 JULY 2017 | VOLUME: 2 | ARTICLE NUMBER: 17120

editorial

Stop neglecting fungi



Fungal pathogens are virtually ignored by the press, the public and funding bodies, despite posing a significant threat to public health, food biosecurity and biodiversity.

https://www.nature.com/articles/nmicrobiol2017120

PUBLISHED: 25 JULY 2017 | VOLUME: 2 | ARTICLE NUMBER: 17120

editorial

Stop neglecting fungi

Indeed, in comparison to the threat from drug-resistant bacterial infections or viral outbreaks, diseases caused by fungi, fungal drug resistance and the development of new antifungal therapeutics gets little coverage. Yet in this case, no news is certainly not good news, and the disparity relative to other infectious disease agents unjustified.

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Few realize that over 300 million people suffer from serious fungal-related diseases, or that fungi collectively kill over 1.6 million people annually, which is more than malaria and similar to the tuberculosis death toll.

The Burden of Fungal Disease (LIFE, 2017); http://go.nature.com/2sMKpuN
Burden of HIV-associated histoplasmosis compared with tuberculosis in Latin America: a modelling study.
Lancet Infect Dis 2018; 18: 1150

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The overall burden of fungal diseases is challenging to quantify, because they are likely substantially underdiagnosed. Kaitlin Benedict K et al., Clin Infect Dis 2018 ciy776,

Disease (most common species)	Location	Estimated life-threatening infections/ year at that location*	Mortality rates (% in infected populations)*
Opportunistic invasive mycoses			
Aspergillosis (*Aspergillus fumigatus*)	Worldwide	>200,000	30–95
Candidiasis (*Candida albicans*)	Worldwide	>400,000	46–75
Cryptococcosis (*Cryptococcus neoformans*)	Worldwide	>1,000,000	20–70
Mucormycosis (*Rhizopus oryzae*)	Worldwide	>10,000	30–90
Pneumocystis (*Pneumocystis jirovecii*)	Worldwide	>400,000	20–80
Endemic dimorphic mycoses*†			
Blastomycosis (*Blastomyces dermatitidis*)	Midwestern and Atlantic United States	~3,000	<2–68
Coccidioidomycosis (*Coccidioides immitis*)	Southwestern United States	~25,000	<1–70
Histoplasmosis (*Histoplasma capsulatum*)	Midwestern United States	~25,000	28–50
Paracoccidioidomycosis (*Paracoccidioides brasiliensis*)	Brazil	~4,000	5–27
Penicilliosis (*Penicillium marneffei*)	Southeast Asia	>8,000	2–75

*Most of these figures are estimates based on available data, and the logic behind these estimates can be found in the text and in the Supplementary Materials. †Endemic dimorphic mycoses can occur at many locations throughout the world. However, data for most of those locations are severely limited. For these mycoses, we have estimated the infections per year and the mortality at a specific location, where the most data are available.

Impact of local epidemiology on global health:
Importation through travel, returned immigrants, global trade
International healthcare, solid organ transplantation, etc.

Brown GD, et al. Sci Transl Med 2012;4;
More updated data: Bongomin F, et al. J Infect 2017;3:57

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World Health Organization

Current WHO Initiatives on fungal infection

- HIV Department have recommendation for screening, treatment, prevention of:
  - Pneumocystis pneumonia
  - *Cryptococcus neoformans*
  - *Candida* (thrush)
- Neglected tropical disease
  - Mycetoma, 2016
  - Chromoblastomycosis, 2017
- Antimicrobial resistance
  - Surveillance of bloodstream infection due to *Candida* spp, 2018

http://www.who.int/glass/events/AMR-in-invasive-candida-infections-meeting/en/

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Unmet Medical Needs

- Increased incidences of invasive fungal diseases in developed countries due to higher survival of susceptible populations
- Remained high mortality/morbidity
- Existing treatment options are limited
  - few antifungal families/targets of action
  - efficacies vary depending on the infecting species
  - pharmacokinetic and –dynamic considerations
- Emergence of antifungal resistance

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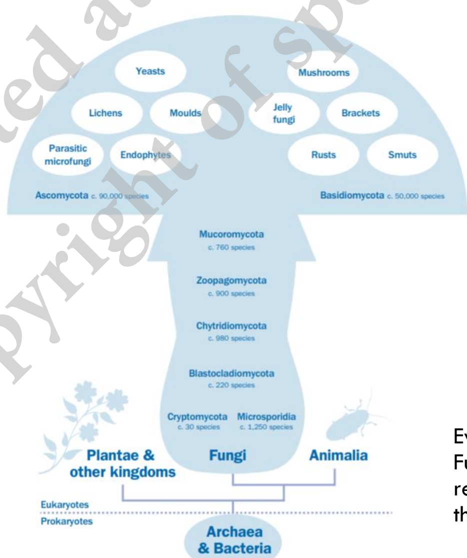
Kingdom Fungi in the Tree of Life



Evolutionary studies have shown that Fungi and Animalia are more closely related to each other than to any of the other kingdoms of life.

https://stateoftheworldsfungi.org/2018/reports/SOTWFungi_2018_Full_Report.pdf

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Global Warming Will Bring New Fungal Diseases for Mammals

- The estimated number of fungal species is 1.5 million, occupying a broad variety of habitats.
- About 300 fungal species are reported to be pathogenic to humans. These fungi have the ability to survive and grow at the high body temperatures of endothermic animals.
- Global warming may increase the prevalence of fungal disease in humans as fungi adapt to survival in warmer temperatures.

Garcia-Solache, M. A., and A. Casadevall. 2010. mBio 1(1):e00061

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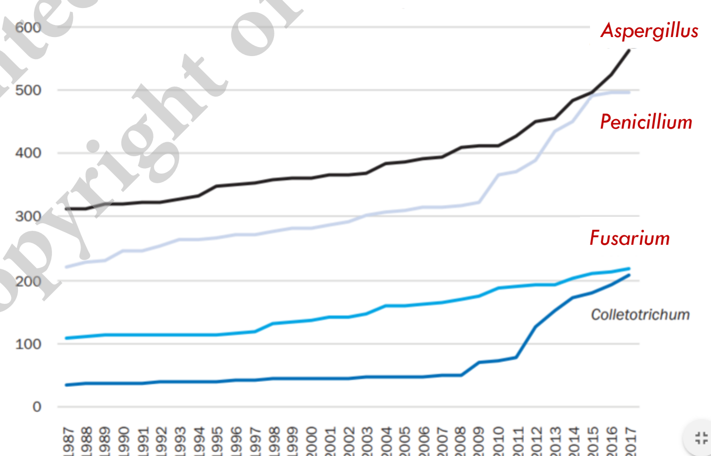
Numbers of accepted species for four economically important fungal genera



https://stateoftheworldsfungi.org/2018/reports/SOTWFungi_2018_Full_Report.pdf

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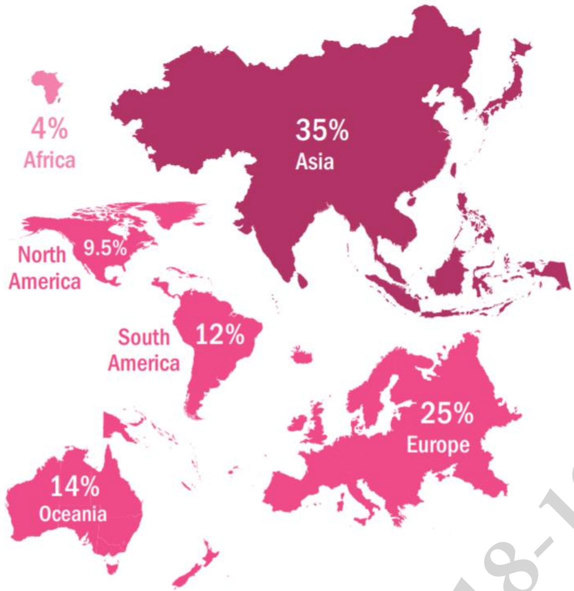

Geographic distribution of new species described in 2017

https://stateoftheworldsfungi.org/2018/reports/SOTWFungi_2018_Full_Report.pdf

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A deadly frog-killing fungus probably originated in East Asia

RISKY TRAVELER A genetic study now traces an amphibian-killing fungus to East Asia, from where international trade in such showy pets as this oriental fire-bellied toad could have helped launch the pathogen worldwide.

https://www.sciencenews.org/article/deadly-frog-killing-bd-fungus-probably-originated-east-asia

S.J. O'Hanlon et al. Recent Asian origin of chytrid fungi causing global amphibian declines. *Science* 2018;360:621.

K. Lips. The hidden biodiversity of amphibian pathogens. *Science* 2018;360:604.

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Emerging: *Candida auris*

The New York Times

April 6, 2019

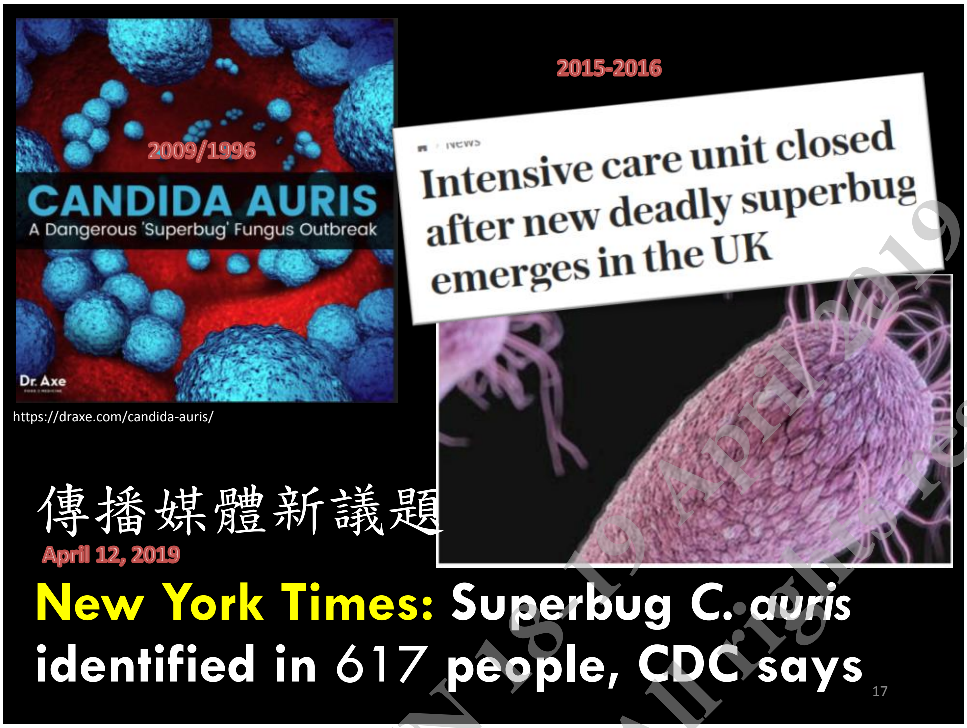
DEADLY GERMS, LOST CURES

A Mysterious Infection, Spanning the Globe in a Climate of Secrecy

> 587 C. *auris* infections since 2013.

Recently C. *auris* reached New York (N=309), New Jersey (N=104) and Illinois (N=144), leading the CDC, USA, to add it to a list of germs deemed "urgent threats."

https://www.nytimes.com/2019/04/06/health/drug-resistant-candida-auris.html


2009/1996
CANDIDA AURIS
A Dangerous 'Superbug' Fungus Outbreak
Dr. Axe
https://draxe.com/candida-auris/
2015-2016
NEWS
Intensive care unit closed after new deadly superbug emerges in the UK
傳播媒體新議題
April 12, 2019
New York Times: Superbug C. auris identified in 617 people, CDC says
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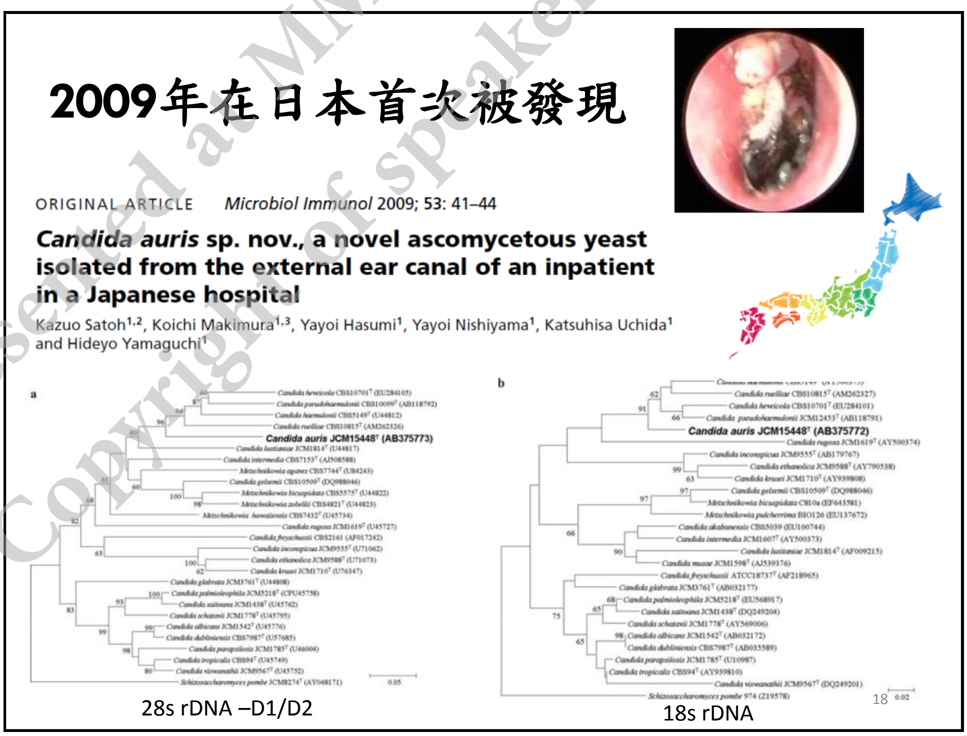
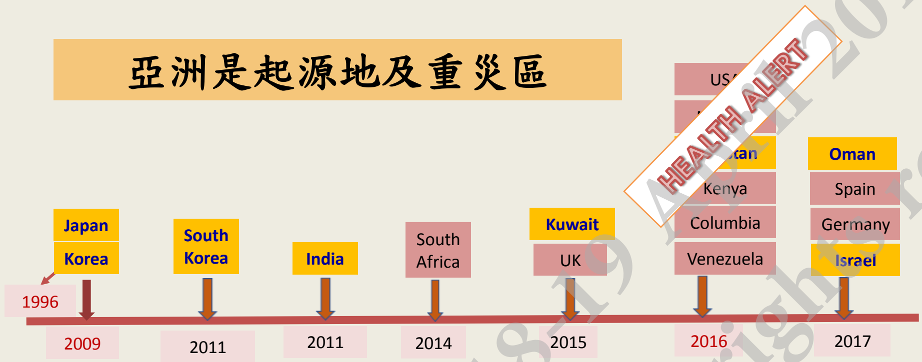

2009年在日本首次被發現
ORIGINAL ARTICLE Microbiol Immunol 2009; 53: 41–44
Candida auris sp. nov., a novel ascomycetous yeast isolated from the external ear canal of an inpatient in a Japanese hospital
Kazuo Satoh1,2, Koichi Makimura1,3, Yayoi Hasumi1, Yayoi Nishiyama1, Katsuhisa Uchida1 and Hideyo Yamaguchi1
a
b
Candida auris JCM15448T (AB375773)
Candida auris JCM15448T (AB375772)
28s rDNA –D1/D2
18s rDNA
18

新興病菌成為全球危機

最早已知的菌株來自於1996 年的南韓，已於歐、亞、 美、非二十餘國迅速傳播並造成感染及重症死亡

亞洲是起源地及重災區



Chakrabarti A, *et al.* Intensive Care Med 2015; 41: 285
Chowdhary A, *et al.* J Hosp Infect 2016; 94: 209

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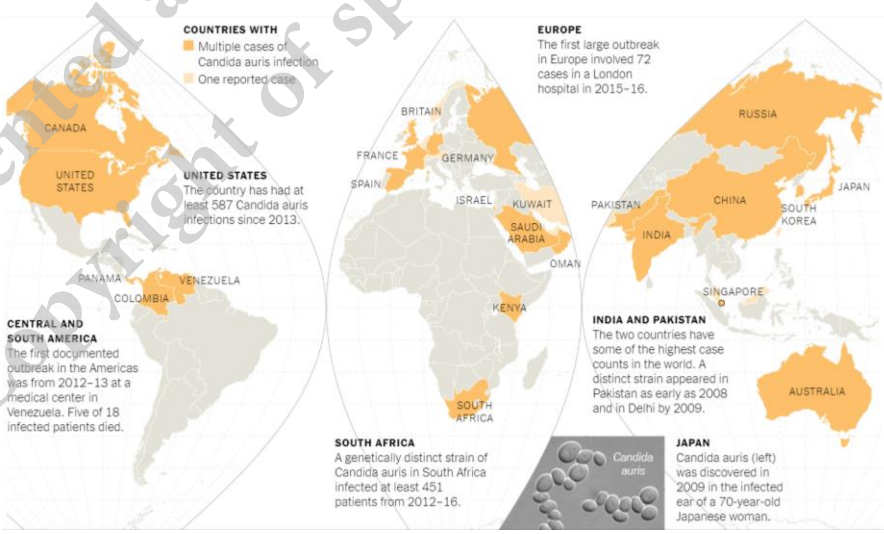
Countries from which C. *auris* cases have been reported



https://www.nytimes.com/2019/04/06/health/drug-resistant-candida-auris.html

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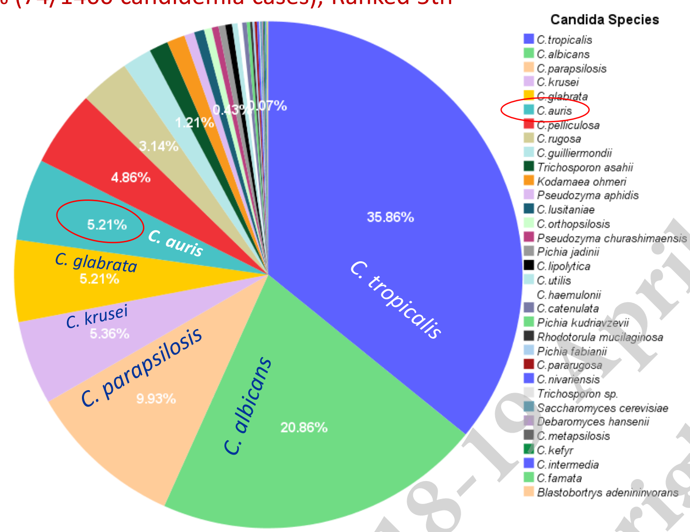
Candidemia, Indian ICUs

The first largest cases series reported

5.3% (74/1400 candidemia cases), Ranked 5th



Chakrabarti *et al.* Intensive Care Med 2015; 41: 285
(President, International Society for Human and Animal Mycology)

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Unique features from largest series in Indian ICUs

- Significant risk factors in Indian ICUs
  1. prior antifungal exposure (P<0.001)
  2. underlying respiratory illness (P<0.002)
  3. vascular surgery (P<0.048)
  4. multiple interventions (P<0.007)
  5. public-sector hospital (P<0.006)

Patients with sepsis, undergoing invasive management for longer periods & exposed to antifungal agents

Rudramurthy S, *et al.* J Antimicrob Chemother 2017; 72: 1794

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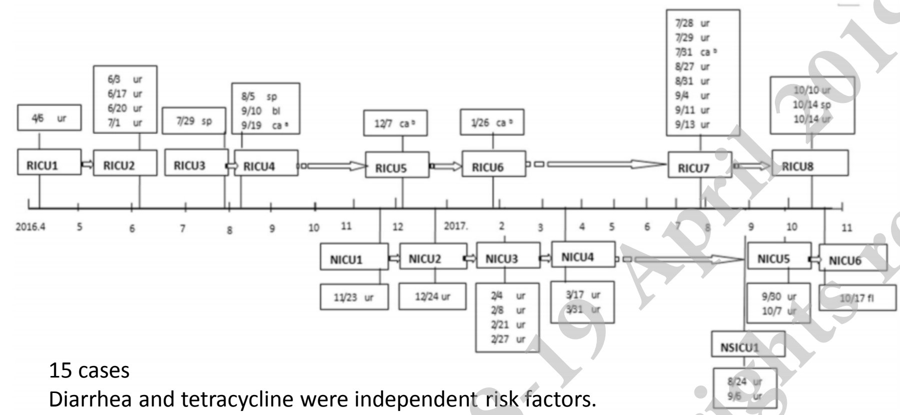
First cases of *C. auris* infection or colonization, Shenyang, China



15 cases
Diarrhea and tetracycline were independent risk factors.

Tian S, et al. Emerg Infect Dis 2018;7:128

RICU, Respiratory ICU; NICU, neuroICU; NSICU, neurosurgery ICU
Sp, sputum; ur, urine; bl, blood; ca, urinary catheter

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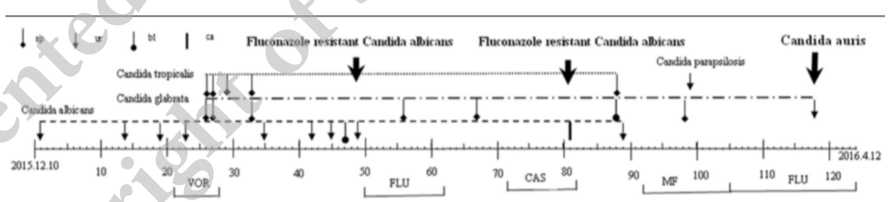
First case, Shenyang, China



Tian S, et al. Emerg Infect Dis 2018;7:128

Vor, voriconazole; FLU, fluconazole, CAS, caspofungin, MF, micafungin;
Sp, sputum; ur, urine; bl, blood; ca, urinary catheter

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Journal of the Formosan Medical Association (2018) 117, 462–470

2017 on line published

Available online at www.sciencedirect.com
ScienceDirect
journal homepage: www.jfma-online.com

Review Article

Are we ready for the global emergence of multidrug-resistant *Candida auris* in Taiwan?

CrossMark

Po-Liang Lu [a,b,c], Wei-Lun Liu [d,e], Hsiu-Jung Lo [f,g], Fu-Der Wang [h,i], Wen-Chien Ko [j,k], Po-Ren Hsueh [l,m], Mao-Wang Ho [n], Chun-Eng Liu [o], Yen-Hsu Chen [a,b,c], Yee-Chun Chen [f,m,*], Yin-Ching Chuang [p], Shan-Chwen Chang [m]

[a] *Division of Infectious Diseases, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan*
[b] *School of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan*
[c] *Department of Biological Science and Technology, College of Biological Science and Technology,*

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Prevalence of *C. auris* among 5064 clinical isolates based on multicenter surveillance in Taiwan

Investigator(s)	Source of isolates	Specimens types	Year	Results
HJ Lo	TSARY National surveillance[b]	Randomly collected *Candida* clinical isolates (1999) or *Candida* isolates from sterile sites and non-sterile sites (2002, 2006, 2010, and 2014)	1999 2002 2006 2010 2014	0/660 0/945 0/1015 0/1130 0/1168
WL Liu, FD Wang, MW Ho, YH Chen, CE Liu	CMMC, VGH-TPE, CMUH, KMUH, CCH	Blood isolates, hospital wide, rare *Candida* species[c]	January 2011–June 2014	0/52[d]
YC Chen, PR Hsueh	NTUH	Blood isolates, hospital wide, rare *Candida* species[c]	2011–2016	0/57[d]
WL Liu	CMMC, Liouying campus	Blood isolates, hospital wide, rare *Candida* species[c]	2007–2014	0/21[d] [37]
MC Li WC Ko	NCKUH	Blood isolates, hospital wide, rare *Candida* species[c]	2011–2016	0/37

Abbreviation: TSARY, Taiwan Surveillance of Antimicrobial Resistance of Yeasts; CMMC: Chi Mei Medical Center; VGH-TPE: Taipei Veterans General Hospital; CMUH: China Medical University Hospital; KMUH: Kaohsiung Medical University Hospital; CCH: Changhua Christian Hospital; NTUH, National Taiwan University Hospital; NCKUH, National Cheng Kung University Hospital.
[a] Data from personal communication with the principal investigators at each hospital or research site. These data are generated based on DNA sequencing of the internal transcribed spacer regions of the nuclear rRNA gene operon and the D1/D2 domain of the large ribosomal subunit of 26S rDNA.
[b] Multicenter in different geographic location of Taiwan.[36]
[c] *Candida* species other than *C. albicans*, *C. tropicalis*, *C. parapsilosis*, *C. glabrata*, and *C. krusei*.
[d] One isolate per patient.

Lu P-L, et al., Are we ready for the global emergence of multidrug-resistant Candida auris in Taiwan?, Journal of the Formosan Medical Association (2017), https://doi.org/10.1016/j.jfma.2017.10.005

The first clinical isolate of *C. auris* in Taiwan

- A 55-year-old man with a medical history of diabetes mellitus and pemphigus vulgaris underwent treatment with azathioprine and prednisolone. Between November 9, 2017 and December 30, 2017, he was hospitalized at CMMC due to pemphigus vulgaris-related skin and soft tissue infection caused by MRSA, and received anti-MRSA treatment.
- On April 11, 2018, several ruptured vesicles with erythematous changes and purulent discharge over the face were noted. Bacterial cultures were obtained.
- *Candida* along with MRSA were recovered from BAP. This isolate did not grow on Mycosel agar containing cycloheximide (400 mg/L) in the culture media that is routinely used for primary isolation of fungi in the laboratory.

Tan HJ, et la. International Journal of Antimicrobial Agents (accepted)

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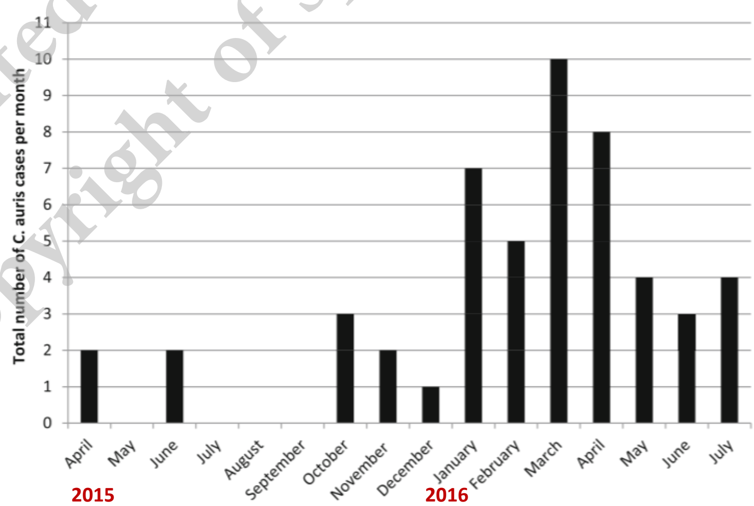
First hospital outbreak *C. auris* in a European hospital



Antimicrob Resist Infect Control 2016;5:35.

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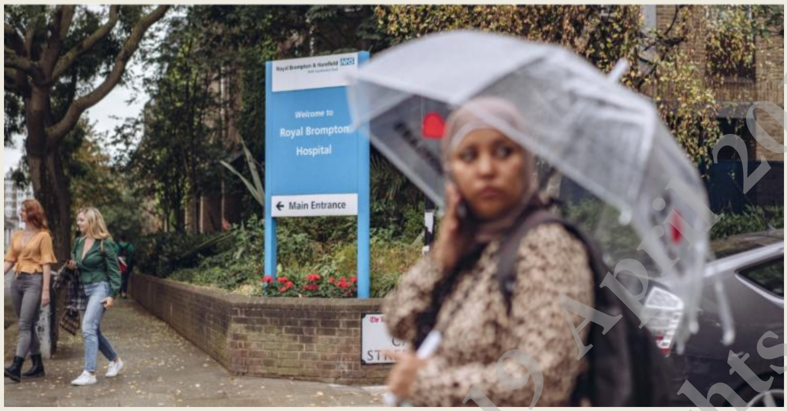
By June 2016, the hospital had seen 72 cases of *C. auris*, and decided to shut down its intensive care unit for 11 days to address the contamination



Royal Brompton Hospital near London, UK - a National Health specialist center for cardio-thoracic surgery with 296 beds that draws wealthy patients from the Middle East and around Europe.

https://www.nytimes.com/2019/04/06/health/drug-resistant-candida-auris.html

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A *Candida auris* Outbreak and Its Control in an Intensive Care Setting

- Oxford University Hospitals, UK; Feb 2015 and Aug 2017
- 70 patients with *C. auris* colonization/infection (7 patients, 10%)
- 94% admitted to the neuroICU before diagnosis
- Predictors of *C. auris* colonization or infection (multivariate analysis)
  - The use of reusable skin-surface axillary temperature probes (odds ratio, 6.80 , P < 0.001)
  - Systemic fluconazole exposure (odds ratio, 10.34, P = 0.01)
- No attributable mortality

N Engl J Med 2018;379:1322

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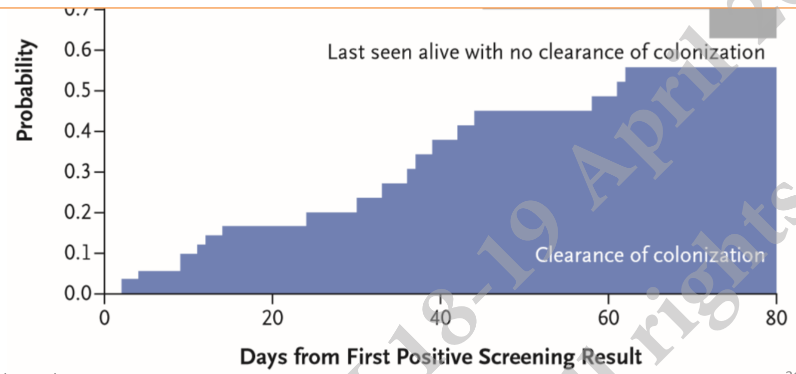
Duration of C. *auris* carriage

The median duration of carriage among patients remaining alive was
- 61 days when two consecutive negative screening results were used to define clearance of colonization
- 82 days when three consecutive negative results were used



N Engl J Med 2018;379:1322

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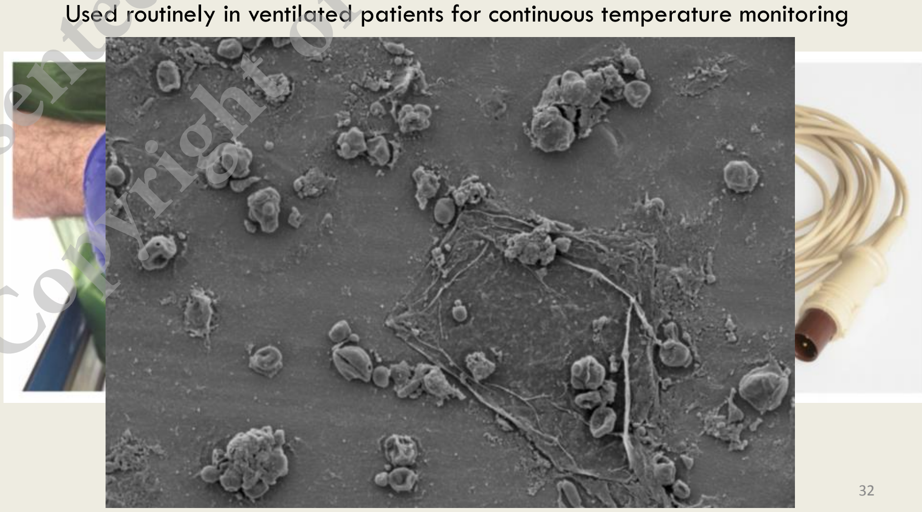
Skin surface temperature probes (axillary), neuroICU, Oxford

Used routinely in ventilated patients for continuous temperature monitoring



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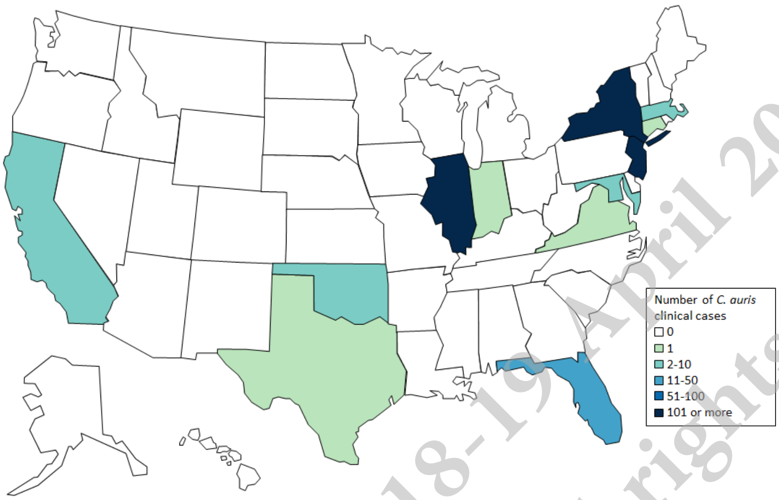
U.S. Map: Clinical cases of *Candida auris* reported by U.S. states, as of February 28, 2019, N=587



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

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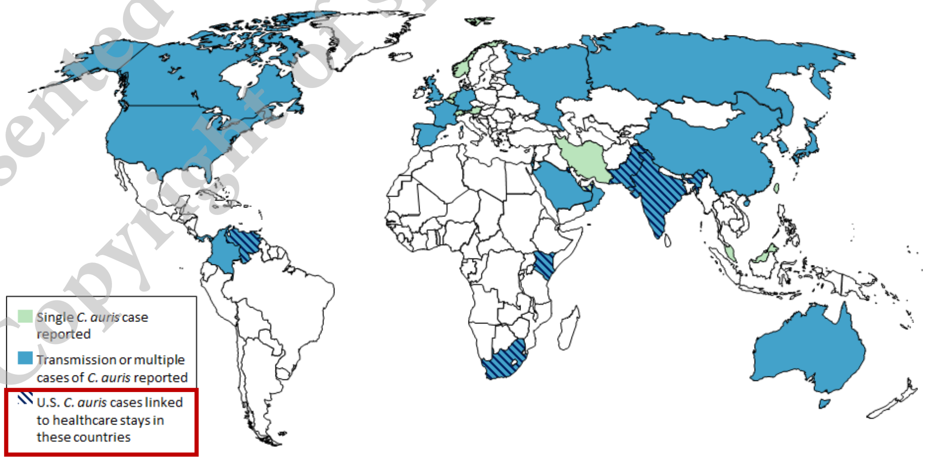
Countries from which *Candida auris* cases have been reported, as of February 28, 2019



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

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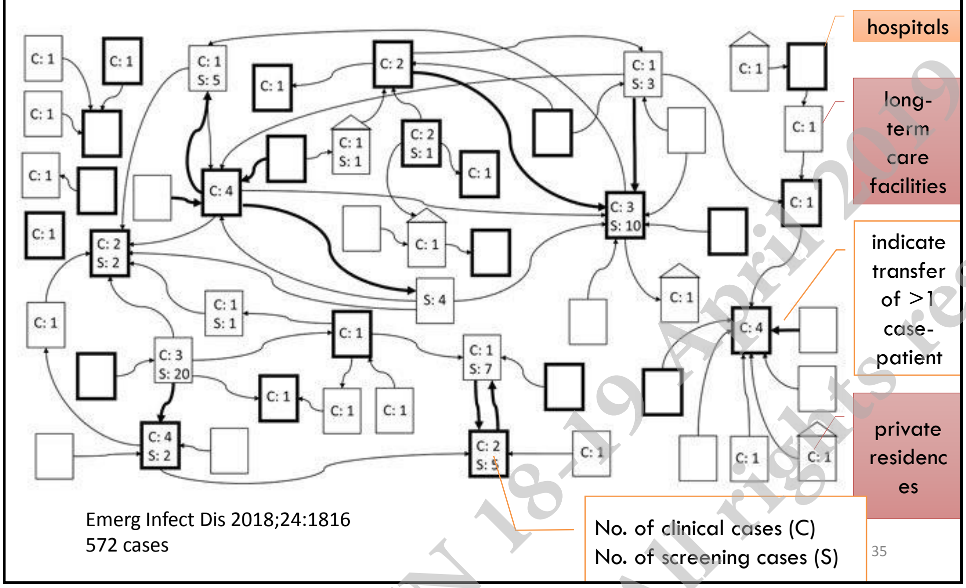
Epidemiologic links between healthcare facilities affected by C. *auris*, New York, USA, 2013–2017



Emerg Infect Dis 2018;24:1816
572 cases

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Environmental contamination with C. *auris* in healthcare facilities, New York, USA

Category, object or surface	No. samples negative by culture & PCR/No. samples evaluated (%)
Near-patient surfaces and objects in rooms	145/178 (82)
Other surfaces and objects in rooms	163/187 (87)
Equipment in room	30/35 (86)
Equipment outside of room	243/260 (94)

Emerg Infect Dis 2018;24:1816

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Everything was positive

Multidrug resistance	Environmental Contamination
Not limited in the acute-care hospitals	Persistent carriage

N Engl J Med 2018;379:1322; Emerg Infect Dis 2018;24:1816

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Common misidentifications based on the identification method used

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

**C. guilliermondii*, *C. lusitaniae*, and *C. parapsilosis* generally make pseudohyphae on cornmeal agar. If hyphae or pseudohyphae are not present on cornmeal agar, this should raise suspicion for *C. auris* as *C. auris* typically does not make hyphae or pseudohyphae. However, some *C. auris* isolates have formed hyphae or pseudohyphae. Therefore, it would be prudent to consider any *C. guilliermondii*, *C. lusitaniae*, and *C. parapsilosis* isolates identified on MicroScan or any *C. parapsilosis* isolates identified on RapID Yeast Plus as possible *C. auris* isolates and forward them for further identification.
https://www.cdc.gov/fungal/candida-auris/recommendations.html

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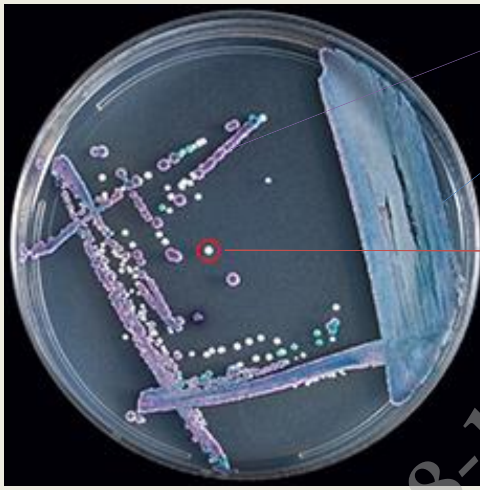
Mixed culture on CHROMagar Candida



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

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Candida auris on CHROMagar Candida, displaying multiple color morphs

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

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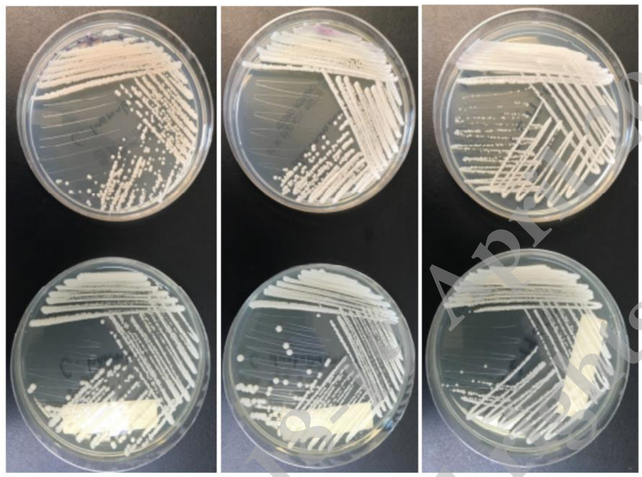
Like most other non-albicans *Candida* species, C. *auris* isolates are germ tube test negative and colonies appear pale purple or pink on CHROMagar Candida medium.

C. auris *C. duobushaemulonii* *C. haemulonii*

CHROMagar

SDA



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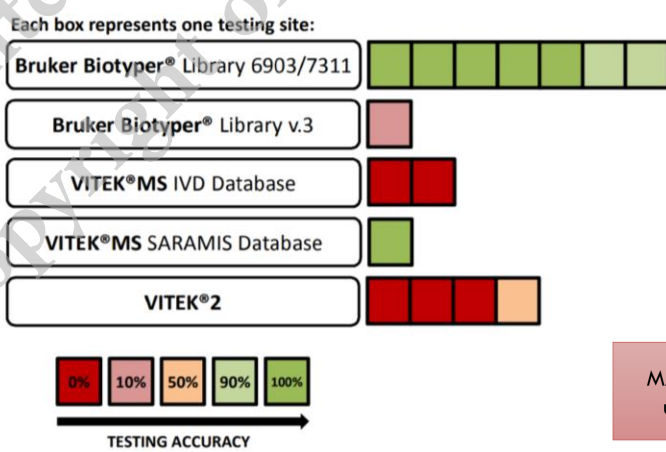
http://www.chromagar.com/fichiers/1526603271AMMI_C_auris_Identification.pdf?PHPSESSID=0541bde3c8c5cdb9fd5caa84968aeabe

The commercially available biochemical test kits and MALDI-TOF instruments used in clinical laboratories for the identification of yeast isolates may lack C. *auris* in their database, these assays may misidentify C. *auris.*



MALDI-TOD MS + update library

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http://www.chromagar.com/fichiers/1526603271AMMI_C_auris_Identification.pdf?PHPSESSID=0541bde3c8c5cdb9fd5caa84968aeabe

National Center for Emerging and Zoonotic Infectious Diseases

Algorithm to identify *Candida auris* based on phenotypic laboratory method and initial species identification

PURPOSE

Candida auris is a multidrug-resistant yeast that has been found in multiple countries, including the United States. *C. auris* can cause invasive infections, be passed from person to person, and persist in the environment. Its severity, communicability, and drug resistance makes correctly identifying *C. auris* crucial to treating patients and preventing infections. However, this is challenging because traditional phenotypic methods frequently misidentify *C. auris*. This algorithm details the steps needed to determine the correct *Candida* spp. based on the tests and equipment available in your lab.

TABLE OF CONTENTS – ALGORITHMS BY METHOD

Please note that these algorithms are based on our current knowledge about misidentification of C.auris and may change as we learn new information.

https://www.cdc.gov/fungal/diseases/candidiasis/pdf/Testing-algorithm-by-Method-temp.pdf

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C. *auris* - an emerging fungus that presents a serious global health threat

https://www.cdc.gov/fungal/diseases/candidiasis/candida-auris-qanda.html

Unique features

1. Is often multidrug-resistant
2. Is difficult to identify
3. Has caused outbreaks in healthcare settings (delayed diagnosis, prolonged carriage, environment contamination)

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Unexpected

Invasive fungal infections after natural disasters

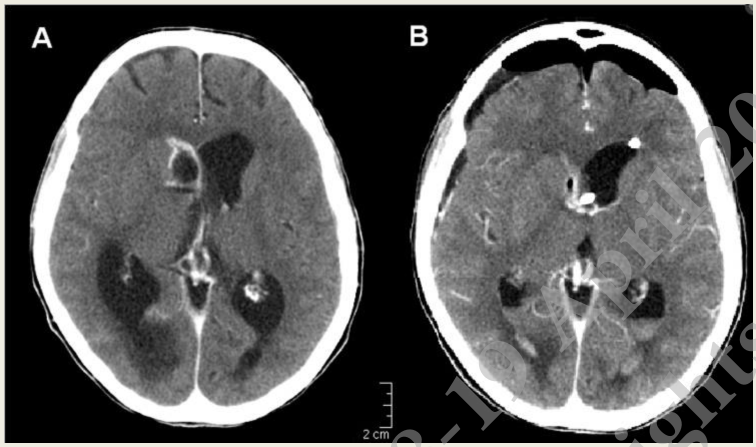
45

Necrotizing fasciitis caused by *Apophysomyces elegans* complicating soft-tissue and pelvic injuries in an Indian Ocean Tsunami survivor, Thailand

42 days liposomal amphotericin B

Snell & Yavakoli Plastic Reconstruct Surg 2007; 119: 448-449

Brain abscess caused by *Scedosporium apiospermum* in a tsunami survivor



Garzoni et al. Emerg Infect Dis 2005;11:1591

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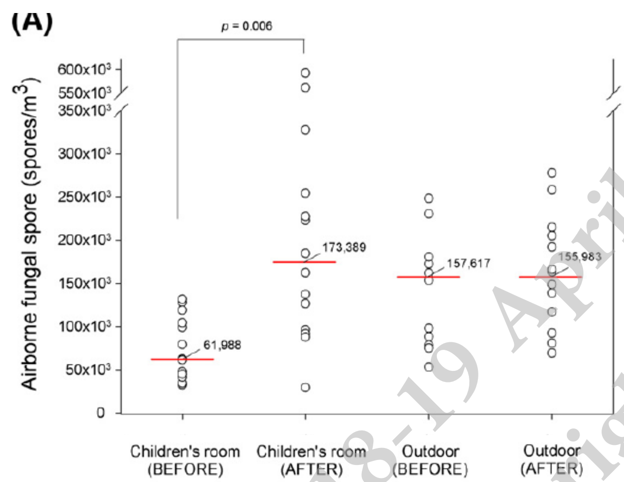
Aspergillus meningitis after the administration of spinal anesthesia for cesarean section after tsunami, Sri Lanka

Characteristic or Test	Patient No. 1	2	3	4	5
Clinical features					
Age — yr	26	21	27	29	38
Date of exposure	June 21	June 22	June 20	June 22	July 17
Date of onset of symptoms	July 3	July 2	July 5	July 3	July 25
Neck stiffness and Kernig's sign†	Absent	+++	++	+	+
Lateral rectus palsy	Absent	Absent	Bilateral	Bilateral	Absent
Stroke	Thalamic infarction on July 9	Thalamic infarction on July 31	Absent	Absent	Ventricular hemorrhage on Aug. 10
Complications	Partial seizures, diabetes insipidus	Partial seizures	Deep-vein thrombosis	Papilledema, hydrocephalus	Coagulopathy, polyuria
Laboratory results					
Random blood glucose — mg/dl	115	90	133	120	109
Cerebrospinal fluid					
Protein — mg/dl	68	49	134	33	28
Glucose — mg/dl	56	25	21	45	61
Neutrophils — no. per mm³	300	400	20	572	0
Lymphocytes — no. per mm³	2	175	700	858	225
Gram's stain	Negative	Negative		Negative	Negative
Cytologic findings	Negative	Negative	Positive for fungal spores	Negative	Negative
Fungal culture of cerebrospinal fluid	Negative	Negative	Negative	*Aspergillus fumigatus*	Negative
Postmortem fungal culture of brain specimen	*A. fumigatus*	*A. fumigatus*			*A. fumigatus*

Gunaratne PS, et al. N Engl J Med. 2007;356:754

Changes in profiles of airborne fungi in flooded homes after typhoon, Taiwan



Hsu et al. Sci Total Environ 2011;409:1677

Percentage profiles of individual fungal species before and after typhoon

Fungal species	Indoor, mean ± SD (%)	
	Before typhoon (n = 11)	After typhoon (n = 11)
Aspergillus niger	0.22 ± 0.38	1.59 ± 2.65
Aspergillus flavus	0.04 ± 0.14	0.00 ± 0.00
Aspergillus glaucus	0.00 ± 0.00	0.10 ± 0.33
Aspergillus versicolor	0.00 ± 0.00	0.83 ± 1.11
Aspergillus terreus	0.00 ± 0.00	9.79 ± 15.30
Aspergillus candidus	0.62 ± 0.85	1.73 ± 3.40
Other *Aspergillus* spp.	0.00 ± 0.00	11.34 ± 15.84
Penicillium	1.62 ± 2.71	1.80 ± 3.62
Cladosporium	34.76 ± 22.91	2.72 ± 5.47
Alternaria	1.16 ± 1.18	0.28 ± 0.92
Paecilomyces	1.22 ± 1.50	4.20 ± 4.62
Curvularia	0.13 ± 0.42	0.00 ± 0.00
Fusarium	0.57 ± 1.52	0.78 ± 1.80
Drechslera	0.66 ± 1.59	0.48 ± 0.88
Non-sporing	43.52 ± 22.65	46.79 ± 22.90
Yeast	14.67 ± 12.98	11.01 ± 10.43
Trichoderma	0.59 ± 0.80	0.00 ± 0.00
Zygosporium	0.00 ± 0.00	0.00 ± 0.00
Unknown	0.23 ± 0.66	6.57 ± 10.20

Hsu et al. Sci Total Environ 2011;409:1677

Invasive fungal infections after natural disasters

- Route of transmission (pattern of infection)
  - Inhalation (respiratory)
  - Trauma (soft tissue infection, CNS)
  - Near-drowning (respiratory)
  - Indoor exposures (respiratory)
  - Healthcare–associated

Benedict & Park. Emerg Infect Dis 2014;20:349

One Health

Agricultural fungicides and invasive fungal infections in humans

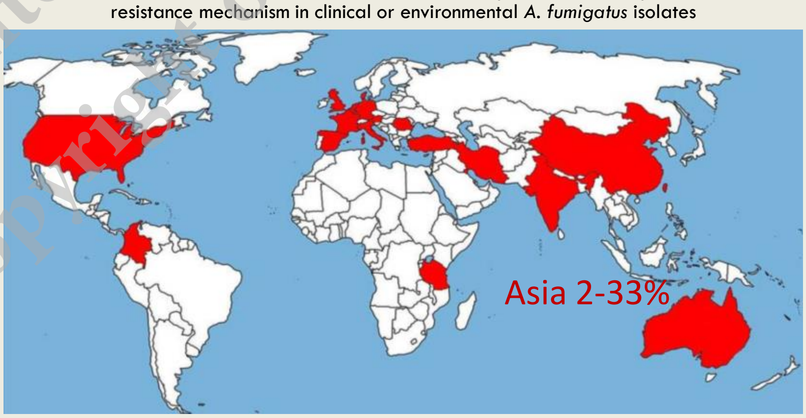
- To minimize agricultural losses from fungal diseases, fungicides are routinely applied to economically valuable crops.
- Although controversial, there is concern that extensive use of agricultural triazoles can induce the resistance of *A. fumigatus* to medically important triazoles such as itraconazole, voriconazole, and posaconazole.
- In the Netherlands, the prevalence of itraconazole resistance of *A. fumigatus* isolated from humans was 6.0%, and 94% of these resistant isolates contain a 34-base pair tandem repeat and a point mutation in *cyp51A* (TR_{34}/L98H mutation). The TR_{34}/L98H mutant also confers reduced susceptibility or resistance to voriconazole and posaconazole. *A. fumigatus* TR_{34}/L98H mutants have also been isolated from humans in several other European countries and Asia.

Gauthier GM, Keller NP. Fungal Genet Biol. 2013 Dec;61:146

Azole Resistance in *Aspergillus fumigatus*

Global 3-6%, Mostly TR34/L98H, which is link to use of azole fungicides

Shaded areas show countries that have reported the TR_{34}/L98H and TR_{46}/Y121F/T289A resistance mechanism in clinical or environmental *A. fumigatus* isolates



Verweij et al. Clin Infect Dis. 2016;62:362; Meis et al. Philos Trans R Soc Lond B Biol Sci. 2016;371(1709).

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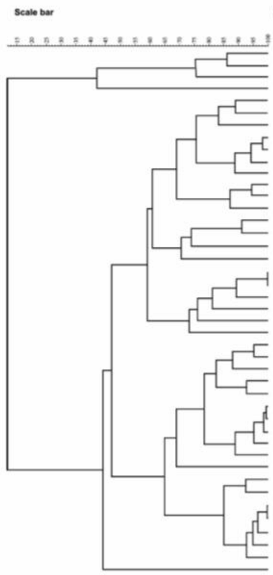
Taiwan and Global *A. fumigatus* isolates



2A	2B	2C	3A	3B	3C	4A	4B	4C	Strains	Phenotype (mutation)	Source	country	Reference
25	23	11	0	9	7	7	10	8	1272/09	Susceptible	Clinical	India	21
25	18	16	9	17	15	12	11	12	A28	Susceptible	Clinical	Southern Taiwan	This study
25	18	16	9	17	15	12	11	0	A26	Susceptible	Clinical	Southern Taiwan	This study
14	11	10	8	22	5	7	7	9	IranSuscep1	Susceptible	Environmental	Iran	20
18	23	15	38	11	48	10	9	8	18512R	Resistant (TR$_{34}$/L98H)	Clinical	France	20
10	16	10	17	13	20	7	5	6	Myc-2008-002 nr.13	Susceptible	Environmental	The Netherlands	20
25	20	20	23	22	33	10	11	10	94/P/10	Susceptible	Clinical	India	20
19	24	15	34	12	26	10	10	12	A13	Susceptible	Clinical	Southern Taiwan	This study
17	27	13	38	12	24	10	9	11	A47	Susceptible	Clinical	Southern Taiwan	This study
10	17	10	25	11	13	7	5	6	BCRC32836	NA	Clinical	USA	17
18	22	10	26	13	23	12	10	5	A25	Susceptible	Clinical	Southern Taiwan	This study
18	24	20	22	13	20	10	10	8	A24	Susceptible	Clinical	Southern Taiwan	This study
17	24	22	24	10	15	10	10	5	A46	Susceptible	Clinical	Southern Taiwan	This study
26	22	25	23	11	22	14	9	8	A35	Susceptible	Clinical	Southern Taiwan	This study
23	12	11	36	25	26	9	11	10	20643.023	Resistant (TR$_{34}$/L98H)	Clinical	China	20
23	12	11	23	23	26	10	10	10	20677.079	Resistant (TR$_{34}$/L98H)	Clinical	China	20
26	12	11	22	10	26	12	10	10	20684.022	Resistant (TR$_{34}$/L98H)	Clinical	China	19
23	11	26	33	17	25	10	11	12	B6	Susceptible	Clinical	Northern Taiwan	This study
19	23	14	30	28	26	12	9	15	B44	Resistant (TR$_{34}$/L98H)	Clinical	Northern Taiwan	This study
19	23	14	30	28	26	12	9	15	B51	Resistant (TR$_{34}$/L98H)	Clinical	Northern Taiwan	This study
16	25	15	35	25	22	12	9	5	B25	Susceptible	Clinical	Northern Taiwan	This study
22	24	25	28	32	21	10	8	8	B22	Susceptible	Clinical	Northern Taiwan	This study
10	16	9	27	35	6	7	5	5	A45	Susceptible	Clinical	Southern Taiwan	This study
12	16	15	23	18	12	12	10	0	B60	Susceptible	Clinical	Northern Taiwan	This study
25	20	19	31	9	10	10	14	5	12-90032258	Resistant (TR$_{34}$/L98H)	Clinical	Australia	19
24	19	20	40	11	7	10	11	7	A16	Susceptible	Clinical	Southern Taiwan	This study
15	19	8	25	10	7	8	9	5	B5	Susceptible	Clinical	Northern Taiwan	This study
18	20	15	42	24	6	9	10	10	20843.017	Resistant (TR$_{34}$/L98H)	Clinical	China	20
19	25	21	34	23	6	10	9	7	A1	Susceptible	Clinical	Southern Taiwan	This study
23	22	16	97	12	7	16	9	10	1962	Resistant (TR$_{34}$/L98H)	Clinical	Germany	19
20	21	11	82	11	7	9	10	11	Myc-2008-002 nr.45	Resistant (TR$_{34}$/L98H)	Environmental	The Netherlands	21
13	10	8	72	9	9	8	9	9	094411/7/50	Resistant (TR34/L98H)	Clinical	The Netherlands	19
25	18	11	55	14	18	12	8	8	A44	Susceptible	Clinical	Southern Taiwan	This study
9	13	17	52	7	23	16	7	5	B52	Susceptible	Clinical	Northern Taiwan	This study
23	19	8	23	13	12	13	7	5	308/E/12/1	Susceptible	Environmental	India	21
20	10	8	35	9	11	8	10	24	Kw1431	Resistant (TR$_{34}$/L98H)	Clinical	Kuwait	19
10	10	8	31	9	7	8	11	24	Myc-2008-002 nr.42	Resistant (TR$_{34}$/L98H)	Environmental	The Netherlands	21
14	21	8	31	9	6	8	10	20	04-202165	Resistant (TR$_{34}$/L98H)	Clinical	Australia	19
14	20	8	32	9	6	8	10	20	Hamid 02	Resistant (TR$_{34}$/L98H)	Environmental	Iran	20
20	21	10	31	11	10	8	10	20	A31	Resistant (TR$_{34}$/L98H)	Clinical	Southern Taiwan	This study
14	24	14	31	9	10	10	10	20	0817960/39	Resistant (TR34/L98H)	Clinical	The Netherlands	20
14	20	9	31	9	10	8	10	28	1042/09	Resistant (TR$_{34}$/L98H)	Clinical	India	21
22	19	17	29	11	20	10	27	5	A18	Susceptible	Clinical	Southern Taiwan	This study

The prevalence rates of azole resistance were 7.9% and 6.5% based on isolates and patients respectively.

Wu CJ et al. Mycoses, 2015;58: 544.

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Azole Resistance in Aspergillus fumigatus: Can We Retain the Clinical Use of Mold-Active Antifungal Azoles?

- An expert panel recommended reconsidering the use of azole monotherapy, i.e., voriconazole, in regions with azole resistance rates exceeding 10%.
- Alternative empirical therapy included either liposomal amphotericin B or voriconazole and echinocandin combination therapy, but the efficacy of these alternative treatment options was the subject of much debate.

Verweij PE, Ananda-Rajah M, Andes D et al. International expert opinion on the management of infection caused by azole-resistant Aspergillus fumigatus. Drug Resist Updat 2015; 21

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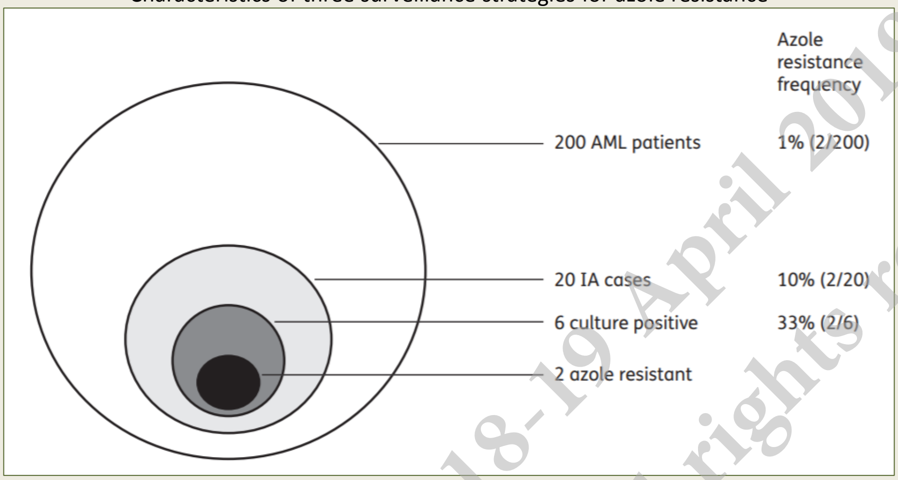
Impact of the denominator on the resistance frequency in azole resistance surveillance

Characteristics of three surveillance strategies for azole resistance



Verweij et al. JAC 2016;71:2079

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Conclusion

Invisible and unexpected

Think fungus

Call for action

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Invisible and Unexpected

Invisible	unaware
What the mind does not know, the eye does not see	Misidentification

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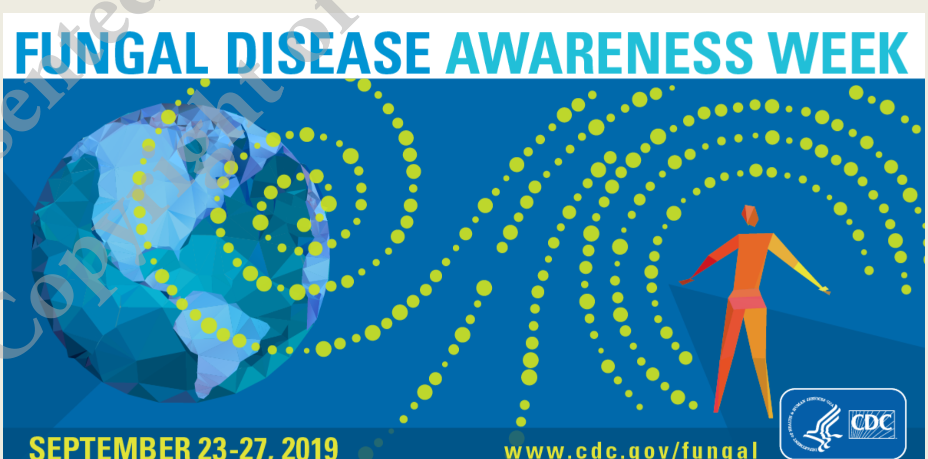
Asia on High Alert for Fungus



https://www.cdc.gov/fungal/awareness-week.html

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Call for Action

Infection prevention and control	Increase in vigilance
Diagnostic stewardship	Strengthen capability and capacity for medical mycology

Need for a One Health strategy

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