# The bad news: Emerging resistant fungi

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ASIA FUNGAL WORKING GROUP an ISHAM working group

ISHAM INTERNATIONAL SOCIETY FOR HUMAN AND ANIMAL MYCOLOGY

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## Disclosures

- Has received research funds from the Ministry of Science and Technology, Taiwan; the Ministry of Health and Warfare, Taiwan; the National Health Research Institutes, Taiwan; National Taiwan University College of Medicine, Taiwan; the Industrial Technology Research Institute, Taiwan; and The University of Alabama for The University of Alabama at Birmingham, USA.
- Receive a grand for clinical trial sponsored by Taiwan Liposome Company, Ltd
- Has received honoraria for speaking or advisory board membership from Gilead, Pfizer, Merck, and Astellas,
- Has involved as a steering committee member of regional education programs from Gilead (Asia CARE) and Pfizer (ISHAM/AFWG/MMTN).

CARE: Continuing Antifungal Research & Education
ISHAM: the International Society for Human and Animal Mycology
MMTN: Medical Mycology Training Network.

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- Under-appreciated
- Under-recognized
- Multiple scenarios
- Conclusion

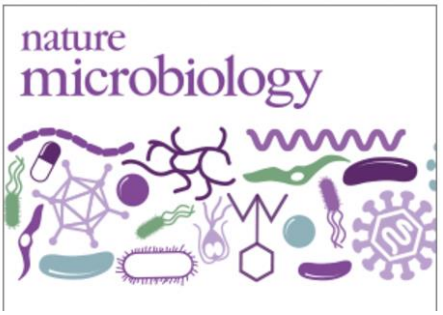


## Under-appreciated

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

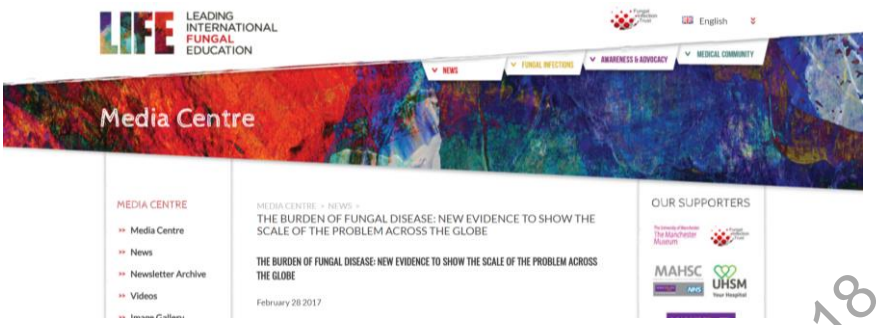


PUBLISHED: 25 JULY 2017 | VOLUME: 2 | ARTICLE NUMBER: 17120

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.




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



## Ten most significant invasive fungal infections

| 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 medicine, solid organ transplantation

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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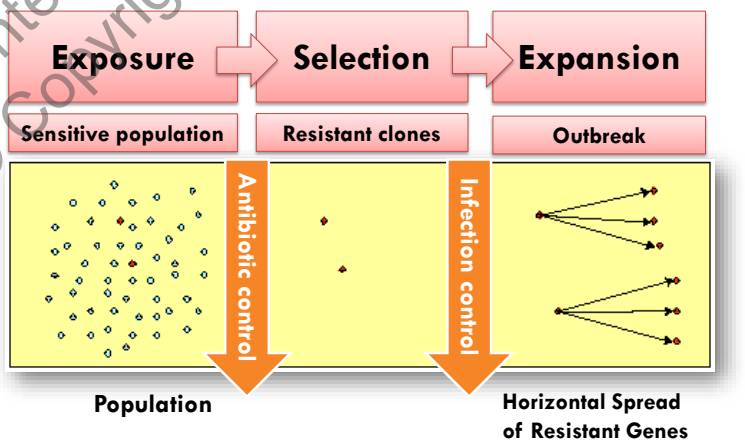
# Unmet medical needs

- 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



# Origins of Antimicrobial Resistance



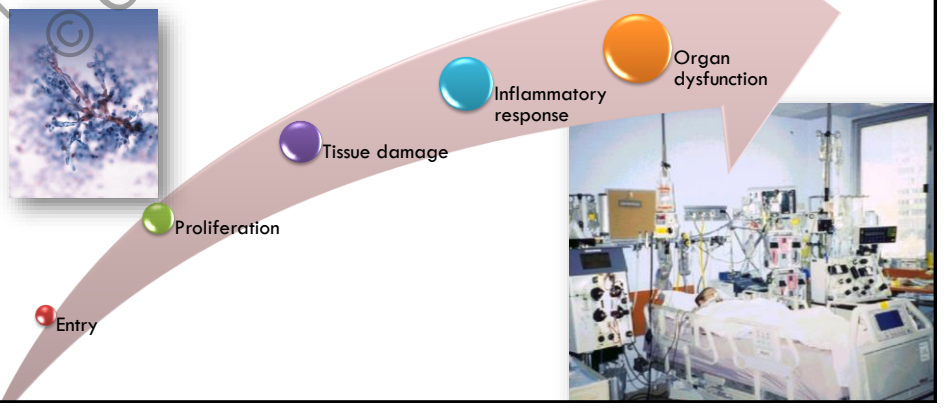

Modified from: Rahal J et al. *JAMA* 1998;280:1233; Landman D et al. *Arch Intern Med* 2002;162:1515

## Under-recognized

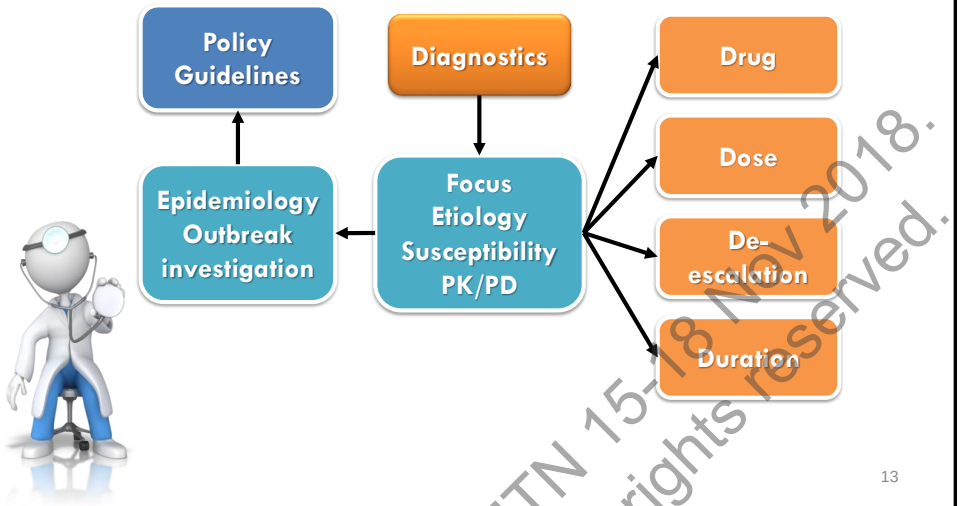


## Very likely underestimated

- ✓**What the mind does not know, the eye does not see.**
- ✓**Expanded spectrum of opportunistic fungal pathogens**



## Diagnosis!!

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*Medical Mycology*, 2017, 0, 1–10
doi: 10.1093/mmy/myx066
Advance Access Publication Date: 0 2017
Original Article

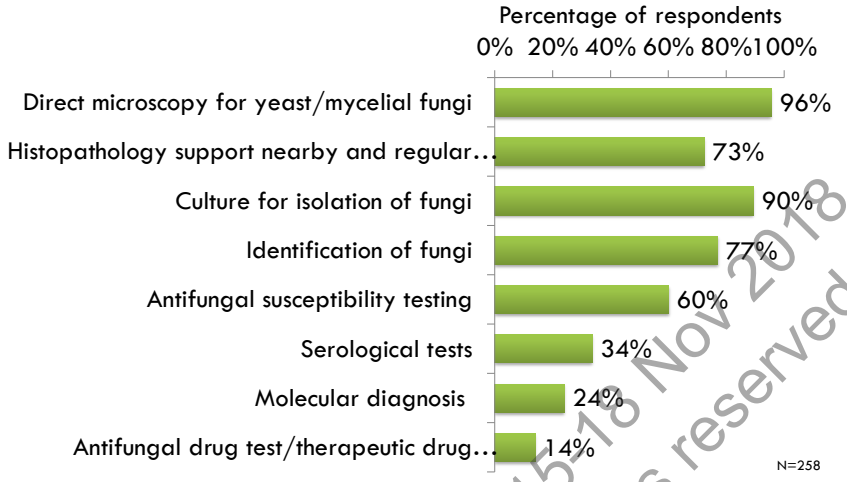
Original Article

# Survey of laboratory practices for diagnosis of fungal infection in seven Asian countries: An Asia Fungal Working Group (AFWG) initiative

Ariya Chindamporn[1], Arunaloke Chakrabarti[2,*], Ruoyu Li[3], Pei-Lun Sun[4], Ban-Hock Tan[5], Mitzi Chua[6], Retno Wahyuningsih[7], Atul Patel[8], Zhengyin Liu[9], Yee-Chun Chen[10] and Methee Chayakulkeeree[11]

[1]Department of Microbiology, Faculty of Medicine, King Chulalongkorn Memorial Hospital Chulalongkorn University, Bangkok, Thailand, [2]Department of Medical Microbiology, Postgraduate Institute of Medical Education & Research, Chandigarh, India, [3]Department of Dermatology, Peking University First Hospital, Research Centre for Medical Mycology, Peking University, Beijing, China, [4]Department of Dermatology, Chang Gung Memorial Hospital, Linkou Branch and College of Medicine, Chang Gung University, Taoyuan, Taiwan, [5]Department of Infectious Diseases, Singapore General Hospital, Singapore, [6]Department of Microbiology and Parasitology, Cebu Institute of Medicine, Cebu, Philippines, [7]Department of Parasitology, Faculty of Medicine Universitas Indonesia, and Department of Parasitology, Faculty of Medicine Universitas Kristen Indonesia, Jakarta, Indonesia, [8]Department of Infectious Diseases, Sterling Hospital, Ahmedabad, India, [9]Department of Infectious Diseases, Peking Union Medical College Hospital, Beijing, China, [10]Department of Internal Medicine, National Taiwan University Hospital and College of Medicine, Taipei, Taiwan and [11]Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

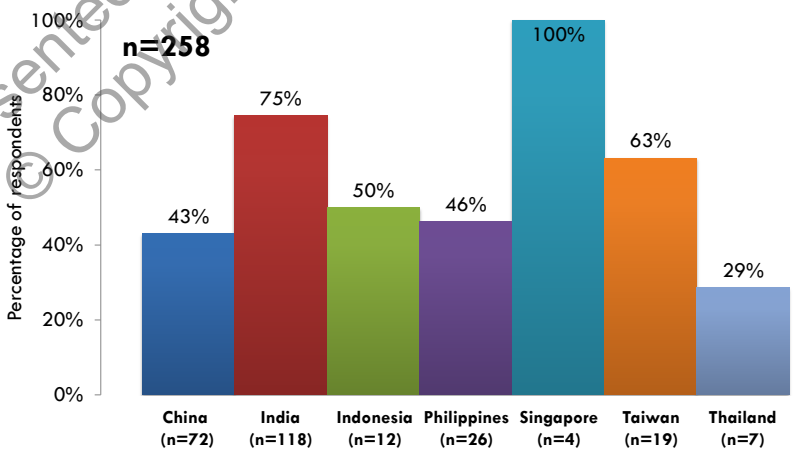
# Diagnostic facilities/services available




N=258 microbiology laboratories

Chindamporn A, et al. Med Mycol. 2018;56:416

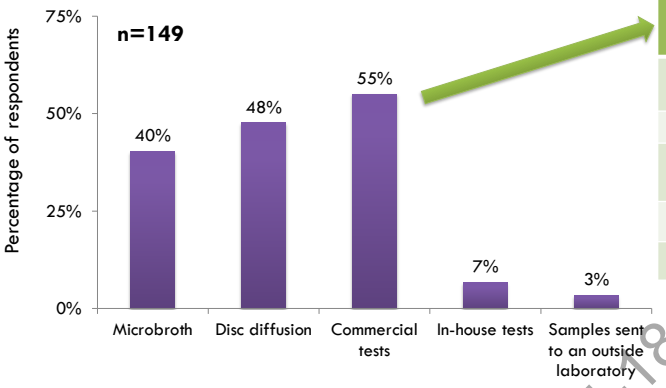
# Antifungal susceptibility testing availability by country




N=258 microbiology laboratories

Chindamporn A, et al. Med Mycol. 2018;56:416

# Antifungal susceptibility testing methods



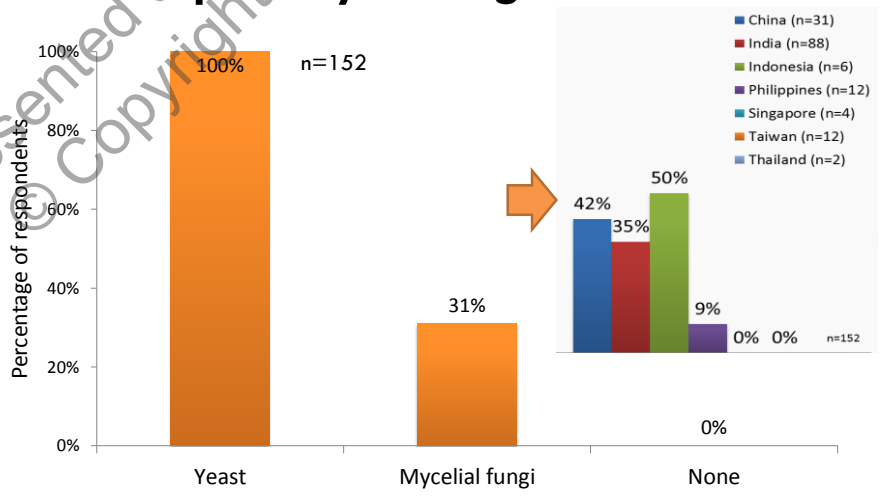

| Commercial tests specified | % of respondents (n=63) |
|---|---|
| VITEK/VITEK 2/VITEK 2 Compact | 61.9% |
| E-test | 20.6% |
| Sensititre/Sensititre YeastOne | 14.3% |
| ATB FUNGUS 3 | 7.9% |
| MIC (not specified) | 4.8% |

N=258 microbiology laboratories

Chindamporn A, et al. Med Mycol. 2018;56:416



# For which organisms is antifungal susceptibility testing available?




N=258 microbiology laboratories

Chindamporn A, et al. Med Mycol. 2018;56:416

## Scenario 1



## Antifungal MICs reported in 2017

| Antifungal | MIC Range, µg/mL | $MIC_{50}$, µg/mL | $MIC_{90}$, µg/mL | Tentative resistant breakpoints |
|---|---|---|---|---|
| Fluconazole | 4–256 | 128 | 256 | ≥ 32 |
| Voriconazole | 0.03–16 | 2 | 8 | NA |
| Itraconazole | 0.125–2 | 0.5 | 1 | NA |
| Posaconazole | 0.06–1 | 0.5 | 1 | NA |
| Caspofungin | 0.03–16 | 0.25 | 1 | ≥4 |
| Anidulafungin | 0.125–16 | 0.5 | 1 | ≥2 |
| Micafungin | 0.06–4 | 0.25 | 2 | ≥4 |
| Flucytosine | 0.125–128 | 0.125 | 0.5 | NA |
| Amphotericin B | 0.38–4 | 1 | 2 | ≥2 |

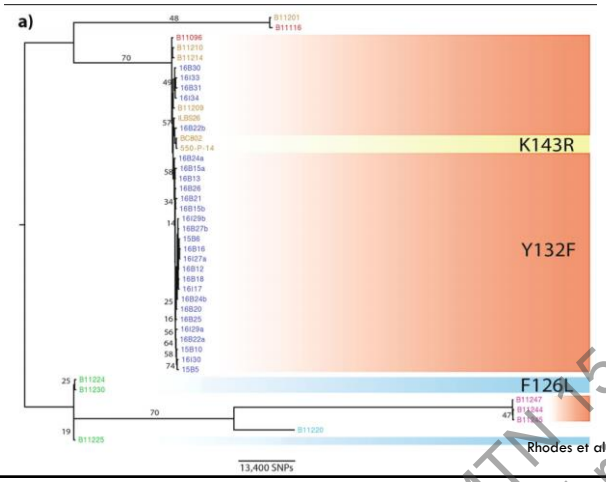
Abbreviations: MIC, minimum inhibitory concentration; $MIC_{50}$, MIC for 50% of isolates; $MIC_{90}$, MIC for 90% of isolates.

- **Resistance to fluconazole (93%), voriconazole (54%), AmB (35%), Echinocandins (7%)**
- **41% ≥ 2 classes**

Lockhart SR, *et al.* Clin Infect Dis 2017; 64: 134
Spivak ES, et al. J Clin Microbiol 56:e01588

# The largest outbreak in the UK occurred in a specialized cardiothoracic London hospital involving 72 patients during 2015/4-2016/11

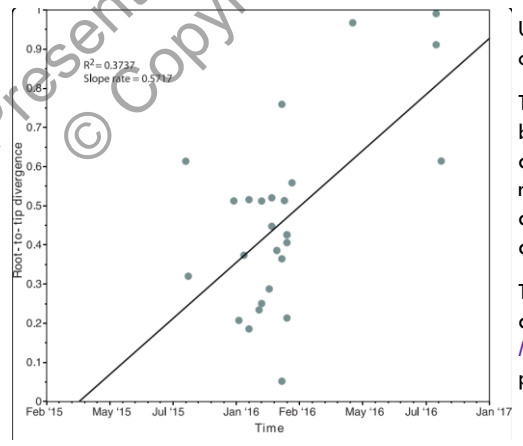
**Phylogenetic analysis of outbreak & global isolates**




Phylogenomic analysis placed the UK outbreak in the India/Pakistan clade. However, there were no known patient travel links of India or Pakistan prior to admission into the hospital.

Rhodes et al. Emerging Microbes & Infections (2018) 7:43

# Clock-like evolution across the timescale of the outbreak




Updated Root-to-tip regression analysis of all 27 outbreak isolates

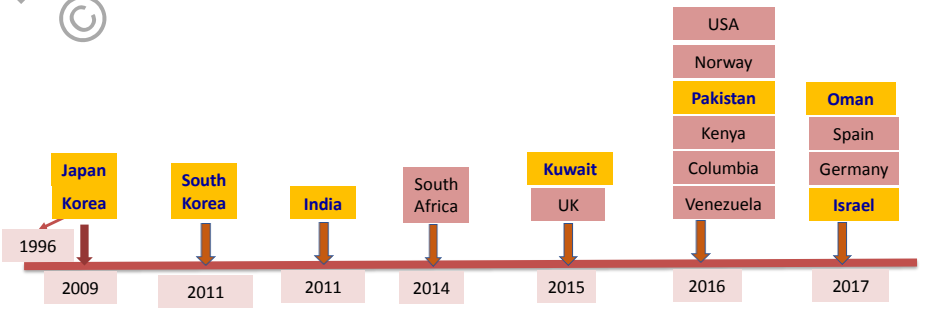
There was a linear relationship between sampling time (measured in days) and the expected number of nucleotide substitutions along the tree, demonstrating clock-like evolution across the timescale of the outbreak.

The time to the most recent common ancestor was estimated to be late March 2015, weeks prior to the first patient identified .

https://www.nature.com/articles/s41426-018-0098-x.pdf



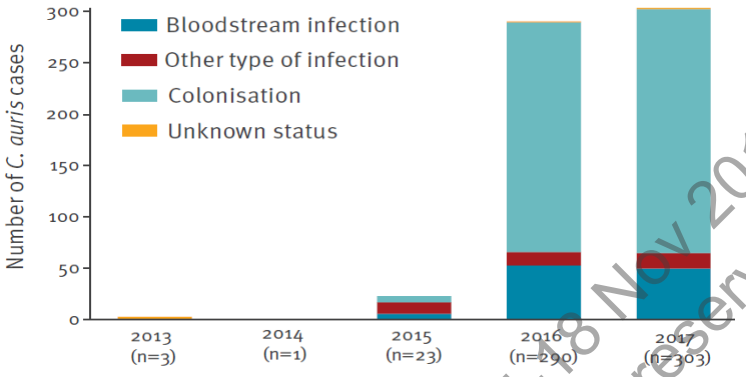

## *Candida auris* - a globally emerging multidrug resistant fungal pathogen




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

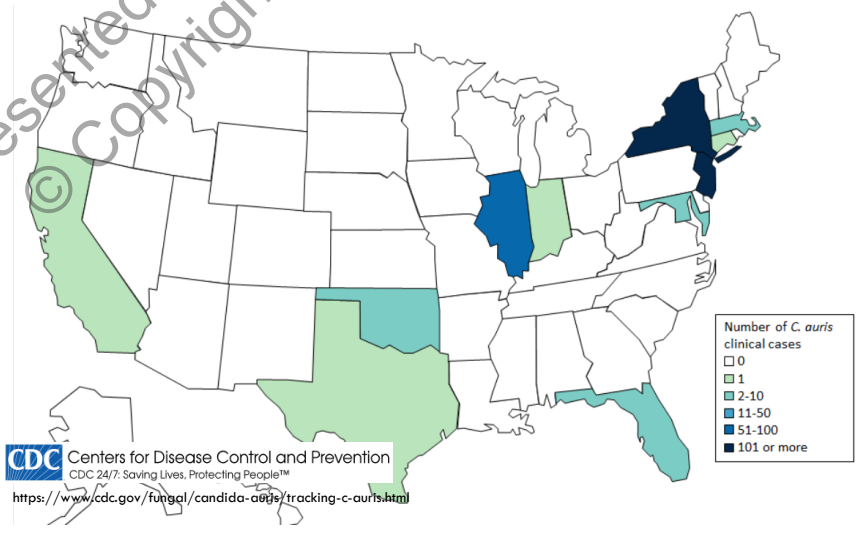
Curtsey of Prof. Chakrabarti A.

## Reported *Candida auris* cases, EU/EEA countries, 2013-2017 (n=620)

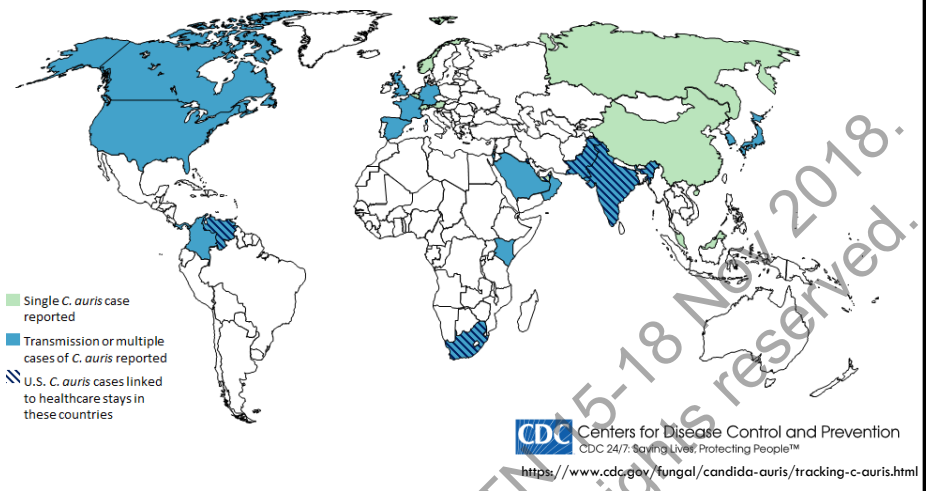



Kohlenberg A, et al. Eurosurveillance 2018;23:pii=18-00136.

## Clinical cases of *Candida auris* reported by state, United States, as of September 30, 2018



## Countries from which *Candida auris* cases have been reported, as of September 30, 2018






## Unique features

1. Difficulties with laboratory identification
2. Propensity to be transmitted in healthcare settings and causing outbreaks
   - Prolonged colonization in patients
   - Persistence in environments
3. Multidrug resistance
4. Causing severe infections and associated high mortality (30-60%)

## Common *Candida auris* misidentifications by commercial biochemical test method

| Biochemical method | Misidentification |
|---|---|
| All methods | *Candida haemulonii*<br>*Candida* spp. not otherwise specified |
| API 20C AUX | *Candida sake*<br>*Rhodotorula glutinis*[b] |
| BD Phoenix | *Candida catenulata* |
| MicroScan | *Candida catenulata*<br>*Candida famata*<br>*Candida guilliermondii*[c]<br>*Candida lusitaniae*[c]<br>*Candida parapsilosis*[c] |
| Vitek2 | *Candida duobushaemulonii*<br>*Candida famata* |

[a]Adapted from https://www.cdc.gov/fungal/diseases/candidiasis/recommendations.html.
[b]When the characteristic red/pink pigment is absent and urease reaction is negative.
[c]When no blastoconidia/pseudohyphae are present on cornmeal agar.

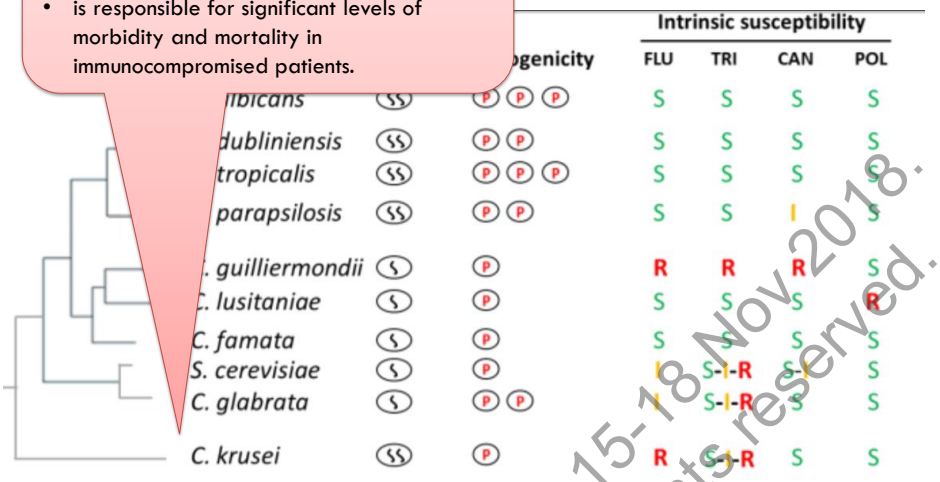
Spivak ES, et al. J Clin Microbiol 56:e01588



## Scenario 2

- has innate resistance to the widely-used drug fluconazole.
- Is one of the five most prevalent causes of candidemia
- is responsible for significant levels of morbidity and mortality in immunocompromised patients.

## nt fungal pathogens




Jensen RH. Dan Med J 2016;63(10)B5288

FLU, fluconazole, TRI, triazoles, CAN, echinocandins and POL, polyenes



# A block of fresh yeast

***Pichia kudriavzevii***

*Pichia kudriavzevii*, *Issatchenkia orientalis* & *Candida glycerinogenes*,
used for industrial-scale production of glycerol and succinate, also used to make some fermented foods.

Population genomics shows no distinction between *Candida krusei* and *Pichia kudriavzevii*: One species, four names

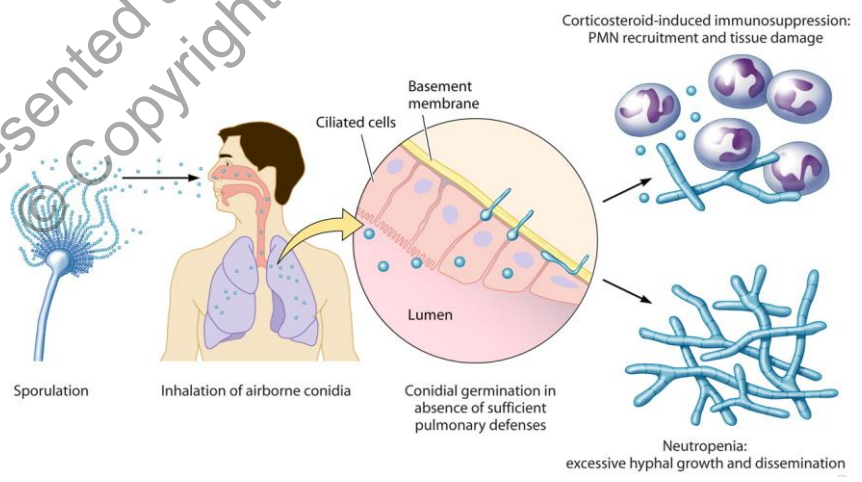
Douglass AP, et al. PLoS Pathog 14(7): e1007138

Azole-resistant *Aspergillus fumigatus*

## Scenario 3



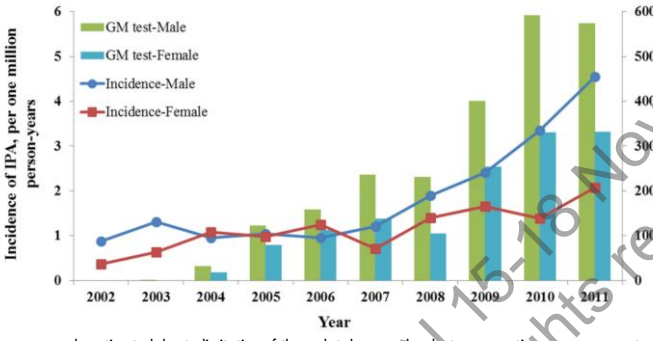
## Infectious life cycle of *A. fumigatus*




Clin Microbio Review 1969

## Incidence of Invasive Pulmonary Aspergillosis: A Nationwide Population-Based Study in Taiwan

- 346 IPA identified from The Taiwan National Health Insurance Research Database, 2002-2011 (1.51 per one million person-years)
- The overall incidence was higher in the 2007–2011period than the 2002–2006 period (0.94 vs. 2.07 per one million person-years, P < 0.0001).

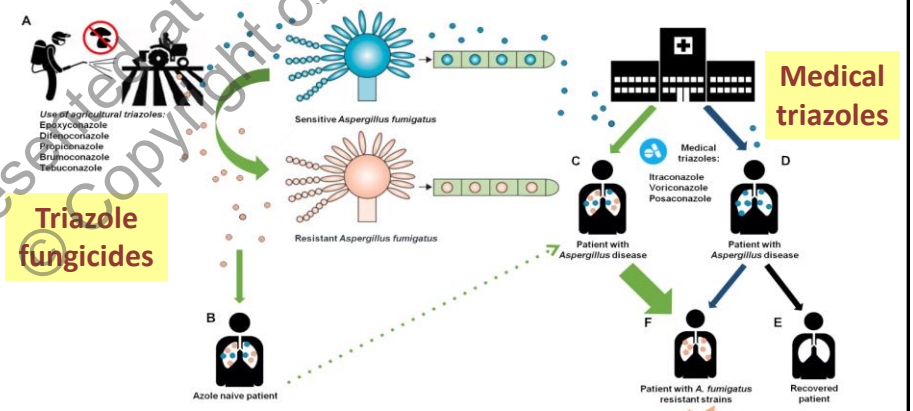



Note. The incidence was underestimated due to limitation of these database and galactomann antigen assay was not widely availabe during the study period.

Sun KS, et al. PLoS ONE 11(2): e0149964



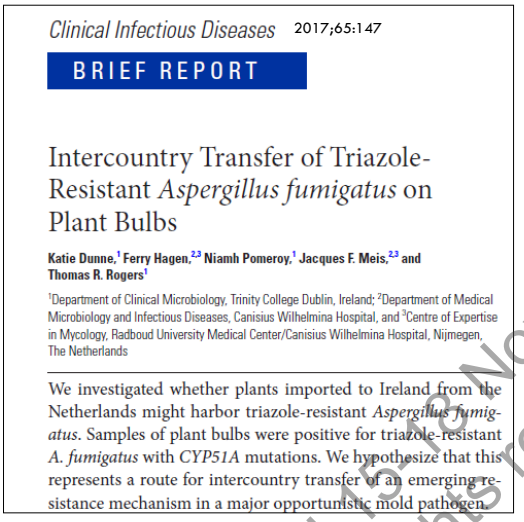
## Routes of azole resistance development in *Aspergillus fumigatus*




| Environmental route | Patient route |
|---|---|
| Cyp51A mutation<br>• $TR_{34}$/L98H<br>• $TR_{46}$/Y121F/T289A | Cyp51A mutation<br>• M220<br>• G54<br>Unknown mechanisms |

Daisuke Hagiwara, et al. Front Microbiol 2017;8:1024

# AMR and global trade



*Clinical Infectious Diseases* 2017;65:147

BRIEF REPORT

## Intercountry Transfer of Triazole-Resistant *Aspergillus fumigatus* on Plant Bulbs

**Katie Dunne,[1] Ferry Hagen,[2,3] Niamh Pomeroy,[1] Jacques F. Meis,[2,3] and Thomas R. Rogers[1]**

[1]Department of Clinical Microbiology, Trinity College Dublin, Ireland; [2]Department of Medical Microbiology and Infectious Diseases, Canisius Wilhelmina Hospital, and [3]Centre of Expertise in Mycology, Radboud University Medical Center/Canisius Wilhelmina Hospital, Nijmegen, The Netherlands

We investigated whether plants imported to Ireland from the Netherlands might harbor triazole-resistant *Aspergillus fumigatus*. Samples of plant bulbs were positive for triazole-resistant *A. fumigatus* with *CYP51A* mutations. We hypothesize that this represents a route for intercountry transfer of an emerging resistance mechanism in a major opportunistic mold pathogen.



Azole-resistant *Candida tropicalis*

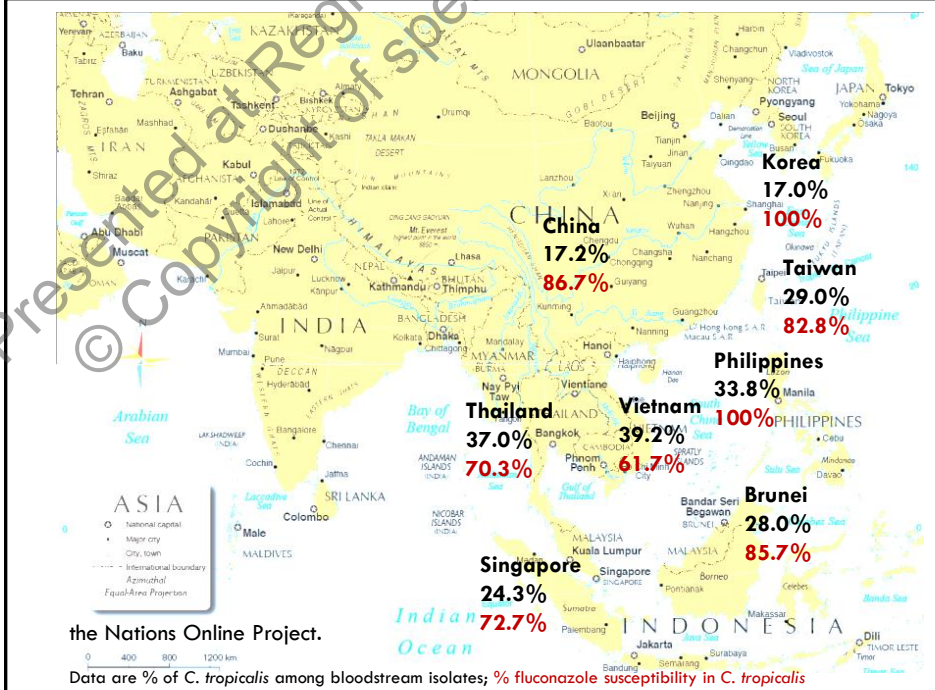
## Scenario 4

# *Candida* and healthcare-associated infections

- USA [1]
  - Multistate point-prevalence survey, 2011
  - The leading pathogens causing healthcare-associated bloodstream infection (22%)
- Taiwan and Korea[2]
  - Nationwide prospective surveillance, intensive care units, 2015
  - Bloodstream infection: 12% and 13%, respectively;
  - urinary tract infection: 31% and 23%, respectively;

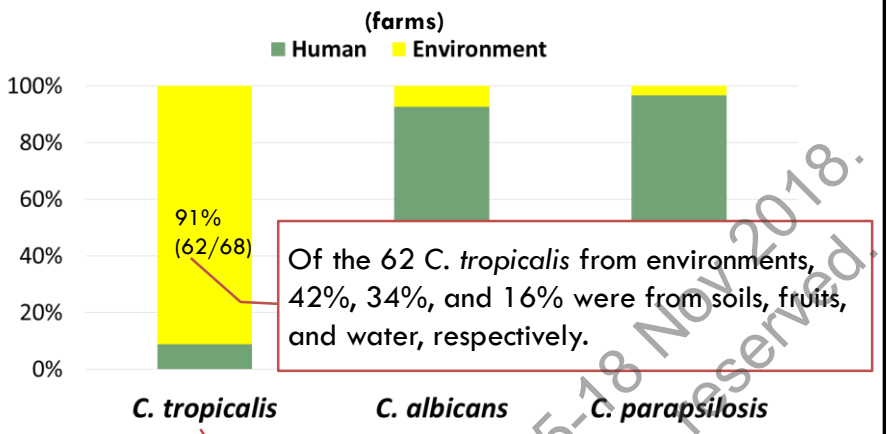
Magill SS, et al. NEJM 2014;370:1198
Chiang CH.. Chen YC. Unpublished data






Data are % of C. *tropicalis* among bloodstream isolates; % fluconazole susceptibility in C. *tropicalis*
Tan et al. Med Mycol 2016;54:471; Xiao M et la. J Clin Microbiol 2018 May 9. (CHIF-NET study, 65 hospitals, 2009-2014)

# Endogenous or exogenous




Of the 62 C. *tropicalis* from environments, 42%, 34%, and 16% were from soils, fruits, and water, respectively.

Of the 68 C. *tropicalis*, 8 (12%) & 22 (32%) were resistant to fluconazole and triadimenol, respectively.

ISHAM 2018, pp2.170; pp4.069 Lo HJ, et al.



# Ecological Traits of *Candida tropicalis*

- Humans: skin or mucous membranes, gut flora[1,2]
- Non-humans:
  - Soil, water [3,4]
  - leaves, raw honey flowers, fruits, fermentation vats [5]
  - Animals [6-8]
- Countries/regions: Taiwan[1,3,4], Brazil[2,5-8]
- C. *tropicalis* isolates obtained from environment/animal sources show resistance to azoles and produce virulence factors [3-8]

1. Chen et al. J Formos Med Assoc 2001;100:791
2. Hoarau et al. mBio 2016;7:e01250
3. Yang et al. PLoS One. 2012;7:e34609.
4. Lo et al. J Infect. 2017;75:254-62.
5. Zuza-Alves et al. Front Microbiol. 2016;7:1783.
6. Álvarez-Pérez et al. Antimicrob Agents Chemother 2016;60:5026
7. Álvarez-Pérez et al. Med Mycol Case Rep. 2016 Feb 2;11:9
8. Cordeiro Rde et al. *Med Mycol. 2015; 53:145*

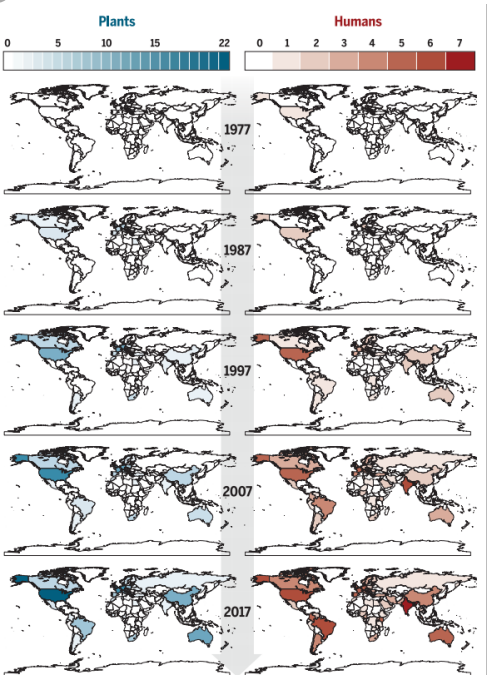
Antifungal resistance: Need for a One Health strategy

# Conclusion



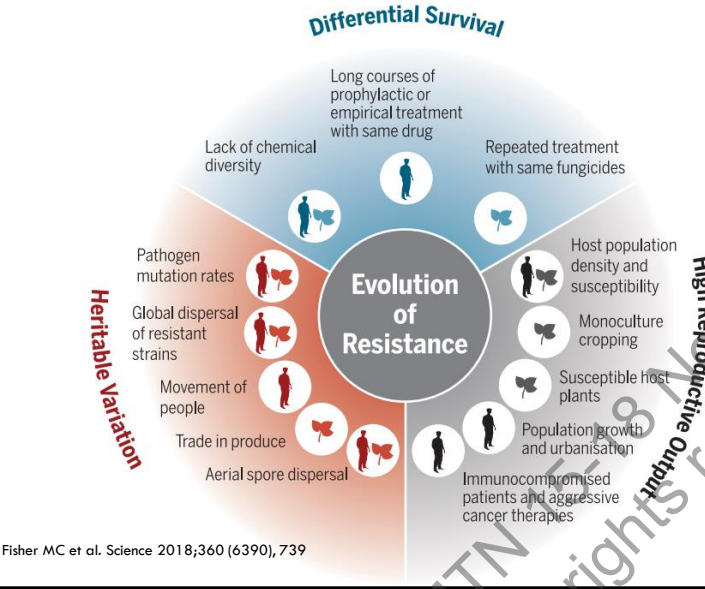
## Fungal species with reported antifungal resistance

Increasing color intensity reflects a growing number of reports. The plant maps depict spatiotemporal records of resistance of crop pathogens to azoles (blue scale). The human maps depict spatiotemporal records of resistance of the pathogens A. fumigatus, C. albicans, C. auris, C. glabrata, Cryptococcus gattii, and Cryptococcus neoformans to azoles (red scale).




Fisher MC et al. Science 2018;360 (6390), 739

## Evolutionary drivers of antifungal resistance




Fisher MC et al. Science 2018;360 (6390), 739



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/

# Call for action

- Strengthen capability and capacity for medical mycology
- Increase in vigilance
- Identify timely the presence of fungal pathogens and antifungal resistance
- Infection prevention and control
- Antimicrobial stewardship
- Need for a One Health strategy