Global incidence and prevalence of aspergillosis and introduction to azole resistance

David W. Denning

The University of Manchester

Global Action For Fungal Infections (GAFFI)

Who gets aspergillosis?
How big a problem is it?

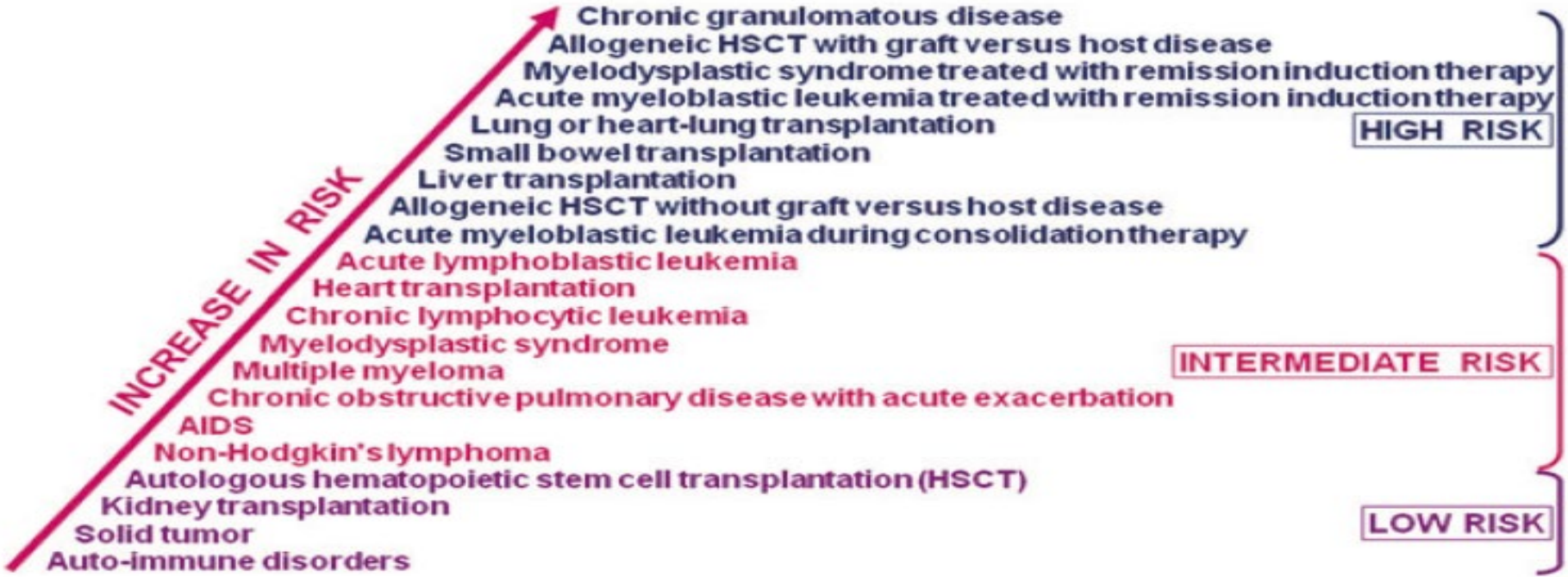
Azole resistance – 19+ years.

Who gets aspergillosis?

A. Invasive

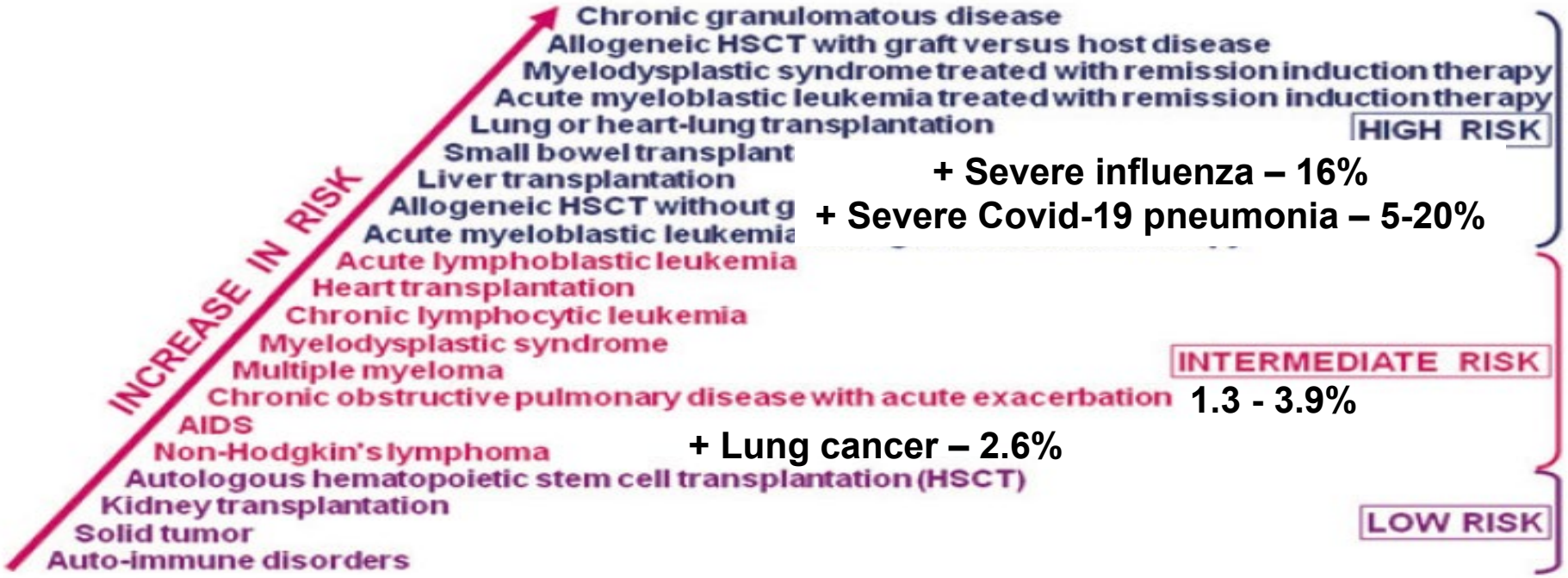
- Immunocompromised people – leukaemia, transplantation, late stage HIV, immunologic disorders, COPD exacerbations, inherited immunodeficiency
- Complex hospitalised patients – ICU, severe influenza or COVID-19

Risk groups and frequencies of invasive aspergillosis – different test performances



Herbrecht, Ann NY Acad Sci 2012;1271:23

Risk groups and frequencies of invasive aspergillosis – different test performances



Herbrecht, Ann NY Acad Sci 2012;1271:23

Invasive aspergillosis in COPD

ORIGINAL ARTICLE MYCOLOGY

Invasive pulmonary aspergillosis in patients with chronic obstructive pulmonary disease: a case control study from China

H. Xu[1], L. Li[1], W.-J. Huang[1], L.-X. Wang[2], W.-F. Li[1] and W.-F. Yuan[1]
1) *Respiratory Medicine and* 2) *Clinical Laboratory, Guangzhou General Hospital of Guangzhou Military Command, Guangzhou, China*

58 of the 298 COPD admissions with a lower respiratory tract sample processed grew *Aspergillus* spp.

39 (3.9%) had probable IA.

Only 13% had oral corticosteroids

43% died

Xu H et al. *Clin Microbiol Infect* 2012;18:403.

New estimate of COPD, admissions to hospital and IA

551,800,000 patients with COPD GOLD stage II-IV
57,938,000 admissions to hospital (10.5% annually)

760,000 IA cases in COPD at a 1.3% rate (Spain)
2,272,000 IA cases in COPD at a 3.9% rate (China)

545,000 – 976,000 deaths predicted annually (43-71%)
UK annual estimate 8,764 IA cases (25,000-30,000 COPD deaths)

Who gets aspergillosis?

A. Invasive

- Immunocompromised people – leukaemia, transplantation, late stage HIV, immunologic disorders, COPD exacerbations, inherited immunodeficiency
- Complex hospitalised patients – ICU, severe influenza or COVID-19

B. Chronic

- After cure of TB
- Confused with TB or TB-like mycobacterial infection
- Other lung disorders – ie COPD, sarcoidosis etc

CPA and TB

CPA can mimic TB.

1. The initial diagnosis of TB is wrong and it is CPA

2. CPA can occur as a co-infection with TB and NTM infections

3. CPA can follow TB as a sequela, especially in those with cavitation at the end of anti-TB therapy

New symptoms after successful TB therapy - ? CPA

Chronic Pulmonary Aspergillosis Situation among Post Tuberculosis Patients in Vietnam: An Observational Study

Ngoc Thi Bich Nguyen [1,*], Huy Le Ngoc [1,*], Nhung Viet Nguyen [1], Luong Van Dinh [1], Hung Van Nguyen [1], Huyen Thi Nguyen [1] and David W. Denning [2,3,*]

54% had CPA

INT J TUBERC LUNG DIS 25(4):324–326

http://dx.doi.org/10.5588/ijtld.20.0735

LETTER

Risk factors for chronic pulmonary aspergillosis in post-TB patients

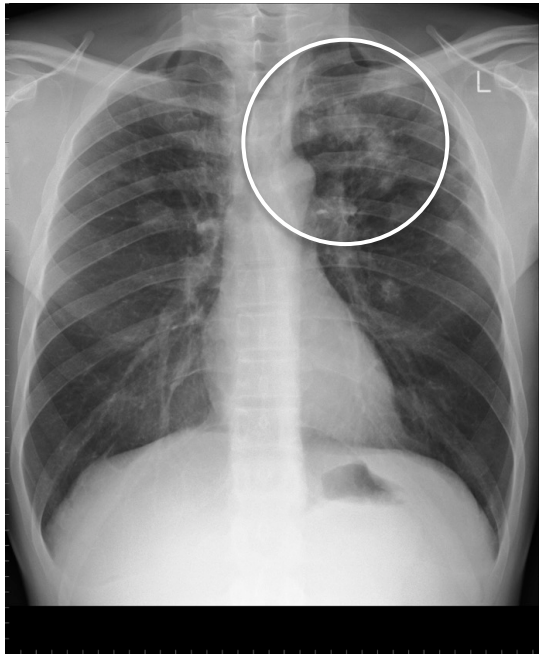
R. Singla,[1] R. Singhal,[2] R. Rathore,[1] A. Gupta,[1] P. Sethi,[1] V. P. Myneedu,[2] A. Chakraborty,[3] V. Kumar[3]

[1]*Department of Tuberculosis and Respiratory Diseases,* [2]*Department of Microbiology, and* [3]*Department of Tuberculosis and Chest Diseases, National Institute of Tuberculosis and Respiratory Diseases, New Delhi, India*

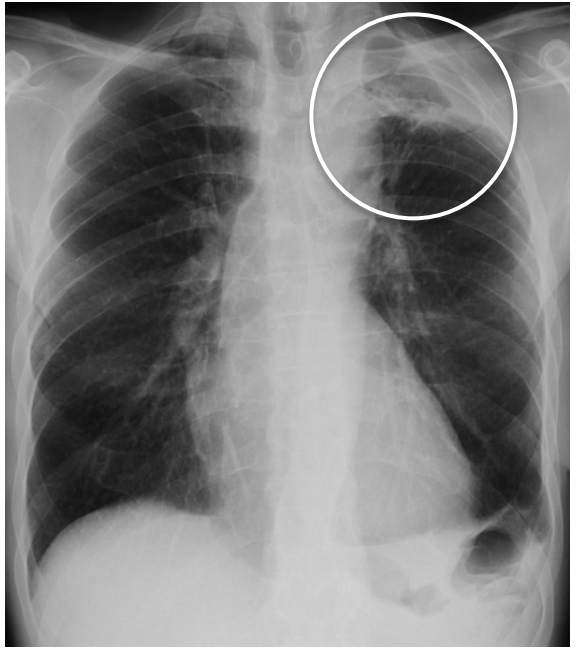
57% had CPA

Singla R et al, Int J TB Lung Dis 2021;25:324; Nguyen N et al, J Fungi 2021;7:532.

TB and aspergillosis chest Xrays similar



Pulmonary tuberculosis



Chronic pulmonary aspergillosis

CPA and TB in India – new modelling

About 2.5 million new lung TB cases a year in India (2020)
~500,000 deaths.
But only 54% were actually confirmed bacteriologically.

Group (India)	CPA cases	Country of origin of data used for extrapolation
Misdiagnosed as TB initially	213,830	Nigeria, Indonesia, Pakistan
In 12 months after TB diagnosis, mimics TB relapse	149,770	Indonesia, Uganda
2-5 years after TB therapy	261,260	UK, Uganda, Korea, Brazil, USA
Annual deaths	143,480	10 countries

Denning DW, submitted for publication and https://gaffi.org/policy-briefs/

Who gets aspergillosis?

A. Invasive

- Immunocompromised people – leukaemia, transplantation, late stage HIV, immunologic disorders, COPD exacerbations, inherited immunodeficiency
- Complex hospitalised patients – ICU, severe influenza or COVID-19

B. Chronic

- After cure of TB
- Confused with TB or TB-like mycobacterial infection
- Other lung disorders – ie COPD, sarcoidosis etc

C. Allergic

- ABPA
- Fungal asthma
- Allergic fungal rhinosinutis

ASPERGILLOSIS	INVASIVE	CHRONIC	ALLERGIC
Global burden	~850,000	1.5M - 3M	6M - 20M
Incidence/100,000	0.6-16	~10.4	?[b]
Prevalence/100,000	—	1.4-126	286[c]
Mortality rate without treatment	~100%	~75%	<1%
Mortality rate with treatment	30-85%	~45%	<1%

Who gets aspergillosis?

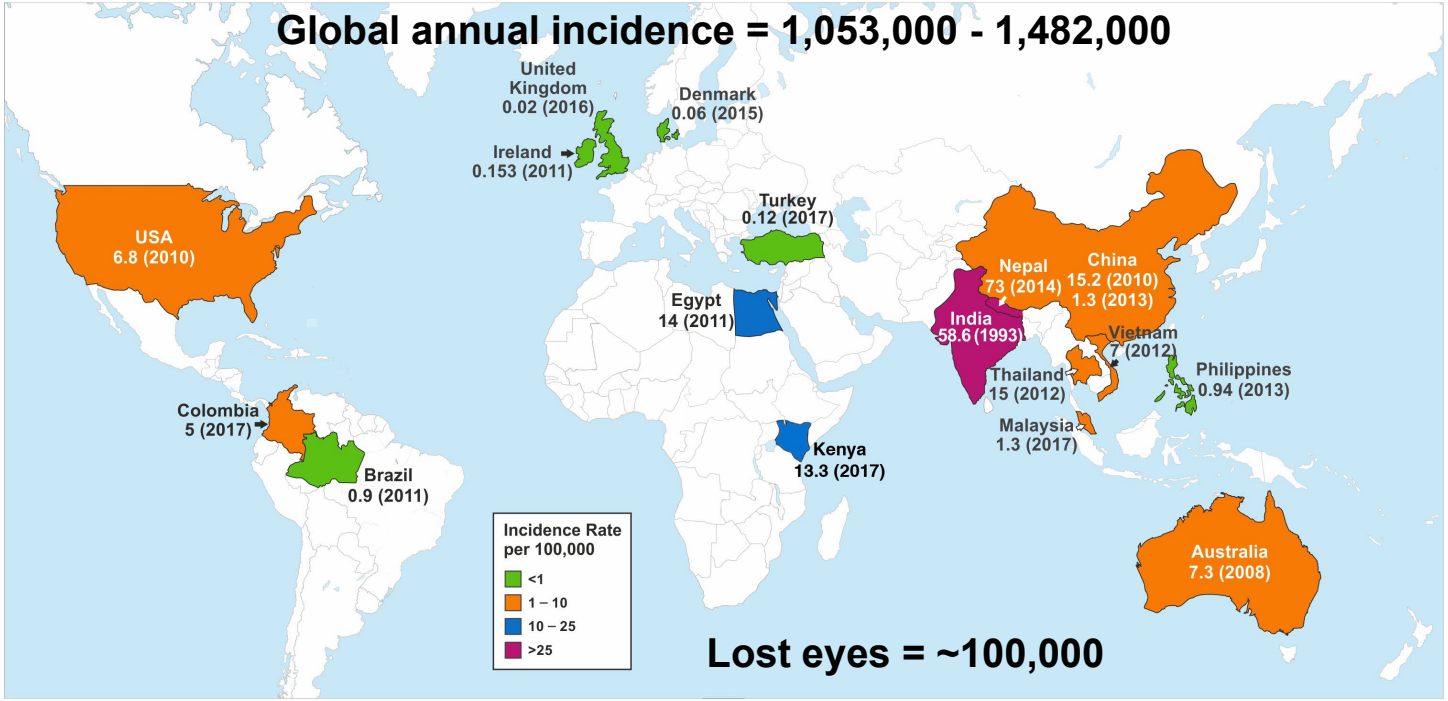
A. Invasive
- Immunocompromised people – leukaemia, transplantation, late stage HIV, immunologic disorders, COPD exacerbations, inherited immunodeficiency
- Complex hospitalised patients – ICU, severe influenza or COVID-19

B. Chronic
- After cure of TB
- Confused with TB or TB-like mycobacterial infection
- Other lung disorders – ie COPD, sarcoidosis etc

C. Allergic
- ABPA
- Fungal asthma
- Allergic fungal rhinosinutis

D. Superficial
- Keratitis
- Onychomycosis
- Otitis externa

Fungal keratitis – estimated annual incidence - ~40% Aspergillus



Brown L et al, Lancet Infect Dis 2021;21(3):e49

www.GAFFI.org

A Review of Onychomycosis Due to *Aspergillus* Species

Felix Bongomin · C. R. Batac · Malcolm D. Richardson · David W. Denning

300 million cases of onychomycosis

- Aspergillus causes <0.5 - 3% of all cases of onychomycosis
- Almost always toenails
- ~10 million cases
- *A. flavus, A. niger &*

A. terreus

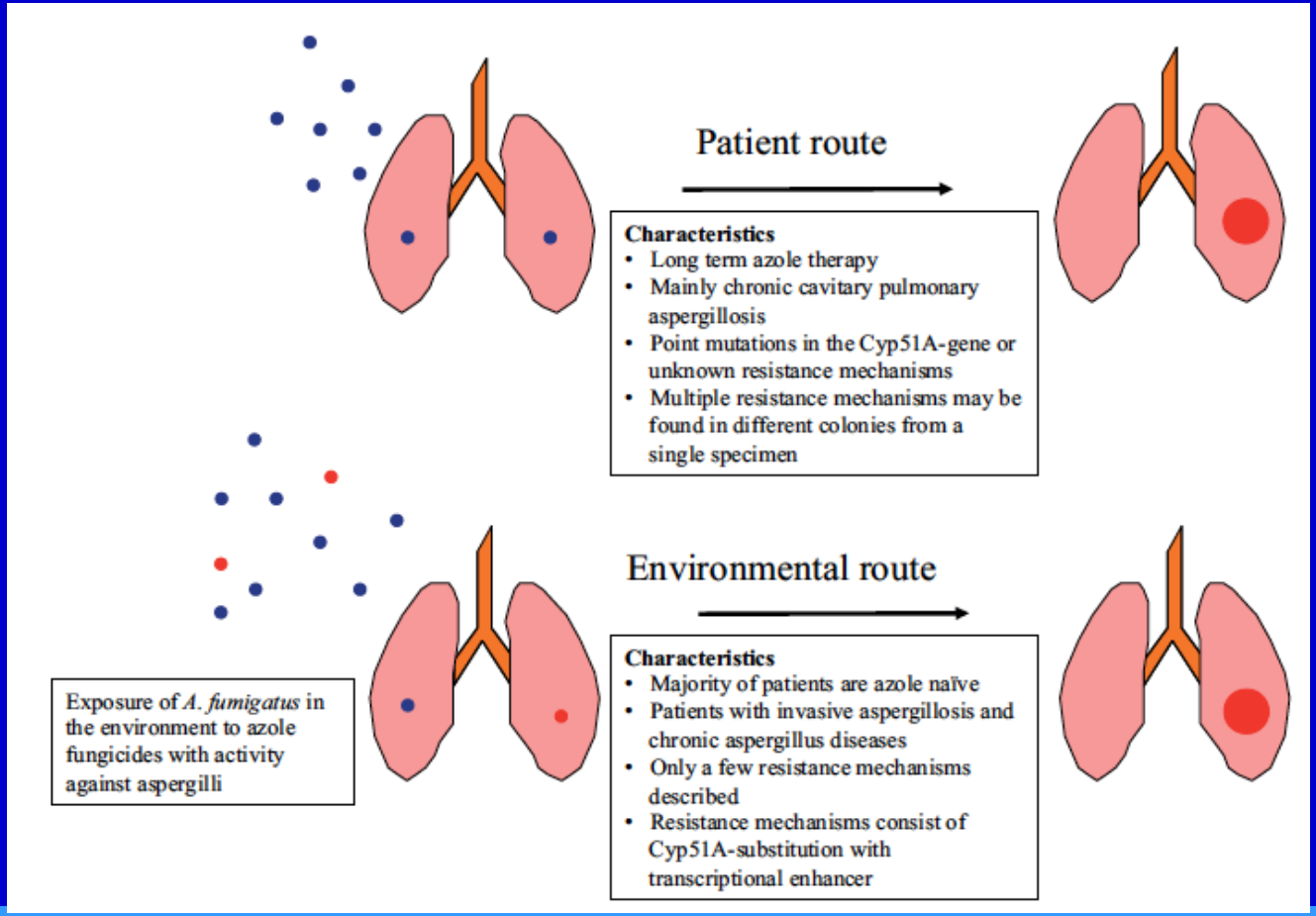
More common in diabetics

Aspergillus otitis externa

- Acute otitis affects 1 in 250 people annually
- Chronic otitis affects 3-5% of the population (200-350 million)
- ~10% are fungal in origin, usually *A. niger*

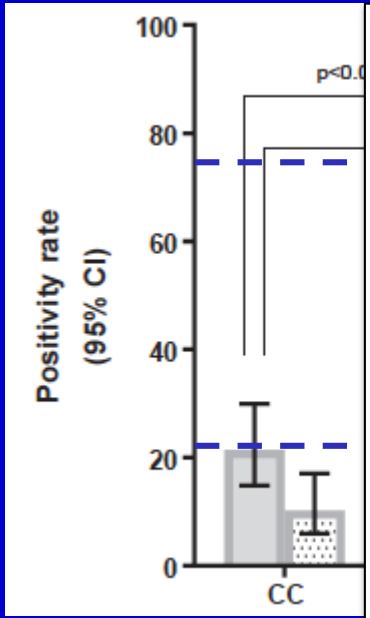
Resistance

Acquisition of resistant *Aspergilli*



Verweij P. Drug Resist Update 2015;21-22:30-40

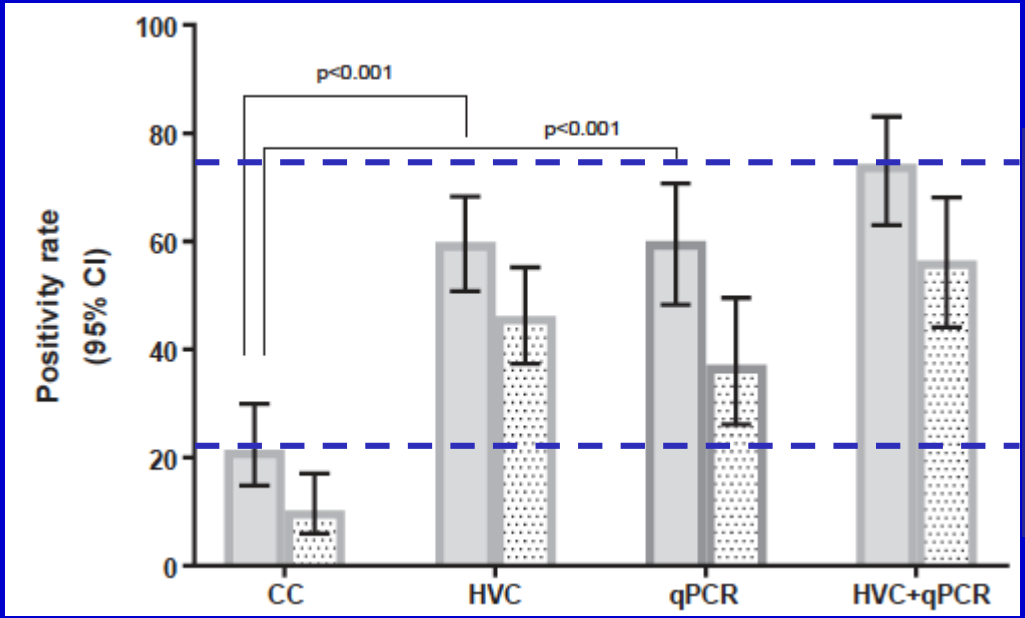
High volume culture and PCR much more sensitive than conventional culture – CPA + ABPA patients



Conventional culture yield for chronic and allergic aspergillosis (bacterial method adopted for fungi)

Vergidis P et al, Clin Microbiol Infection 2020;26;935

High volume culture and PCR much more sensitive than conventional culture – CPA + ABPA patients

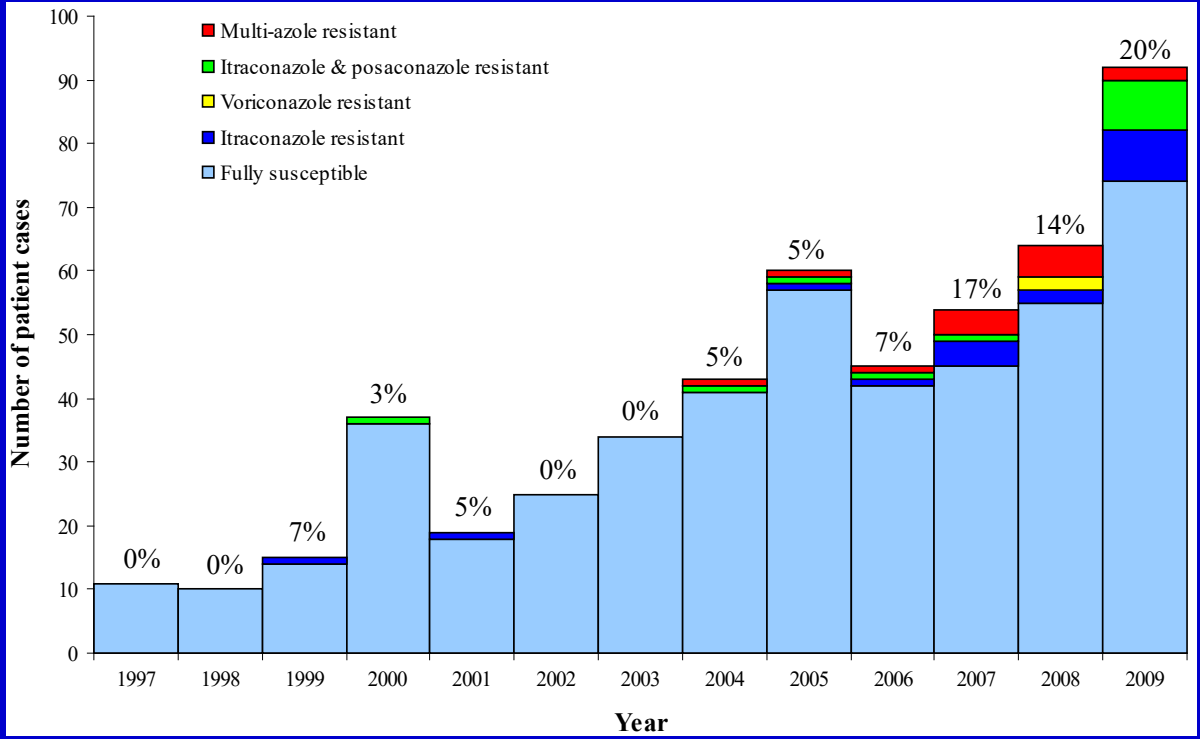


76% in CPA

20.6% in CPA

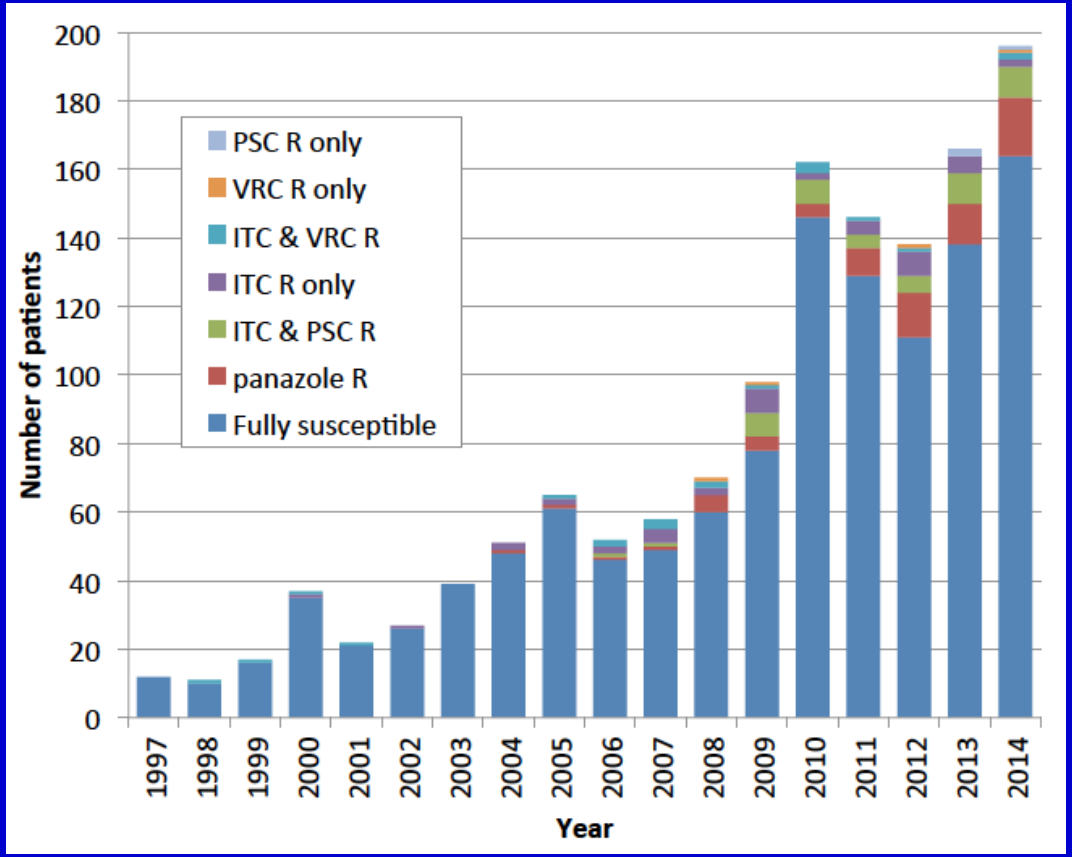
Vergidis P et al, Clin Microbiol Infection 2020;26;935

Azole resistance in *A. fumigatus* in Manchester 1997-2009



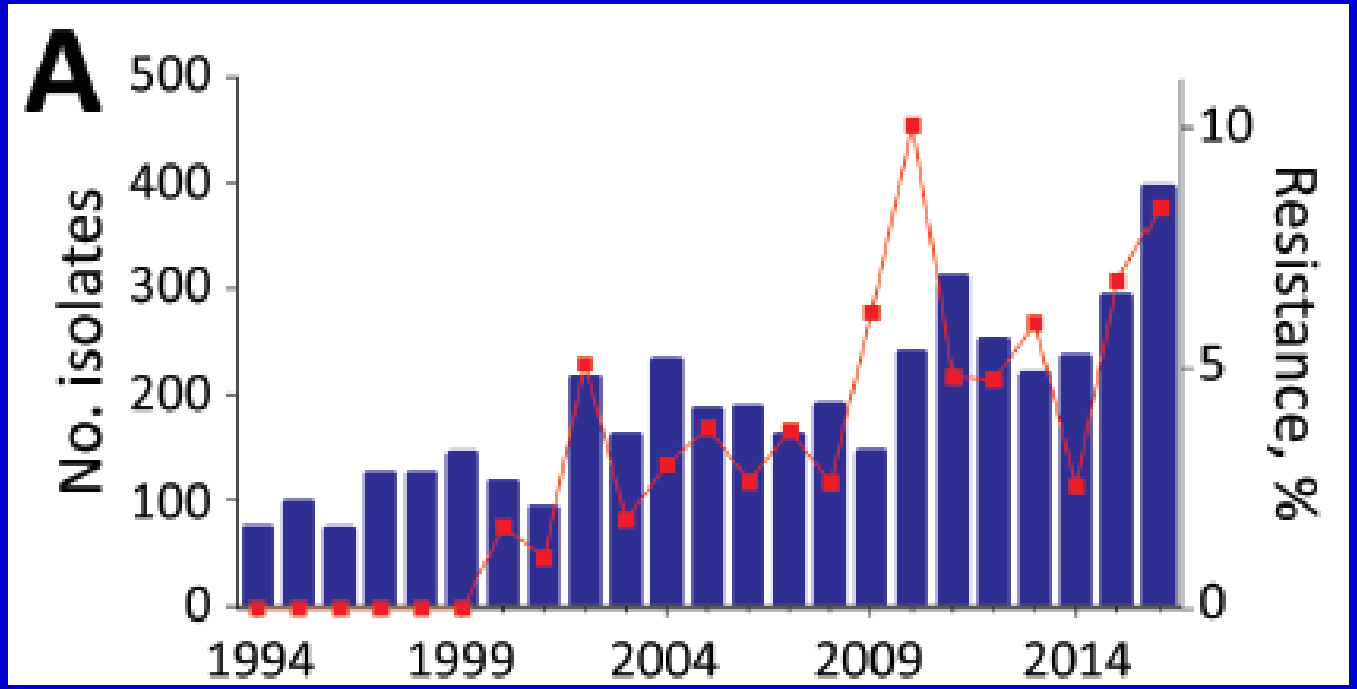
Bueid, J Antimicrob Chemother 2010;65:2116. Howard et al, EID 2009; 15:1068

Azole resistance in *A. fumigatus* - 2010-2014



National Aspergillosis Centre, unpublished

Azole resistance in *A. fumigatus* in Netherlands - 1994-2016



Buil JB, Emerg Infect Dis 2019;25:176

Clinical Infectious Diseases

INVITED ARTICLE

HEALTHCARE EPIDEMIOLOGY: Robert A. Weinstein, Section Editor

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

Paul E. Verweij,[1] Anuradha Chowdhary,[2] Willem J. G. Melchers,[1] and Jacques F. Meis[1,3]

[1]Department of Medical Microbiology, Radboud University Medical Centre, Nijmegen, The Netherlands; [2]Department of Medical Mycology, Vallabhbhai Patel Chest Institute, University of Delhi, India; and [3]Department of Medical Microbiology and Infectious Diseases, Canisius Wilhelmina Hospital, Nijmegen, The Netherlands

+ Japan, Canada, Morocco and others

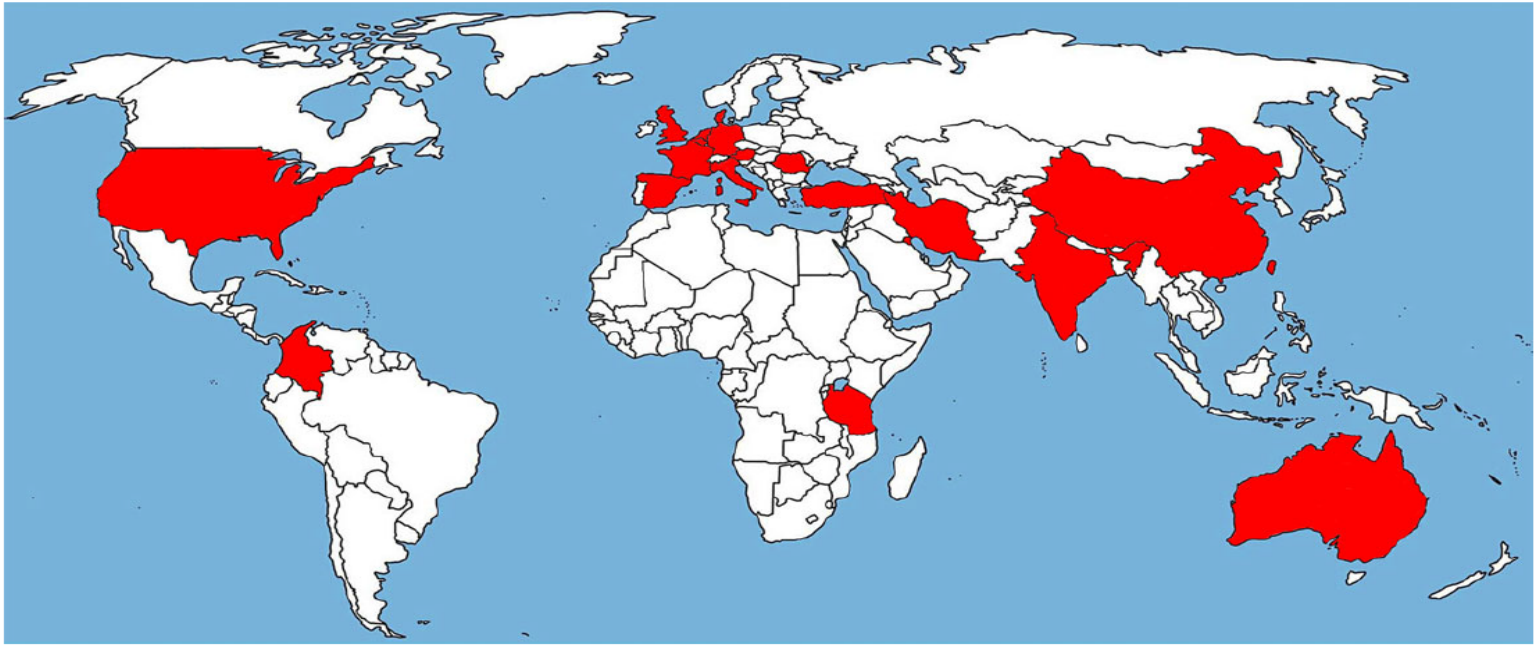
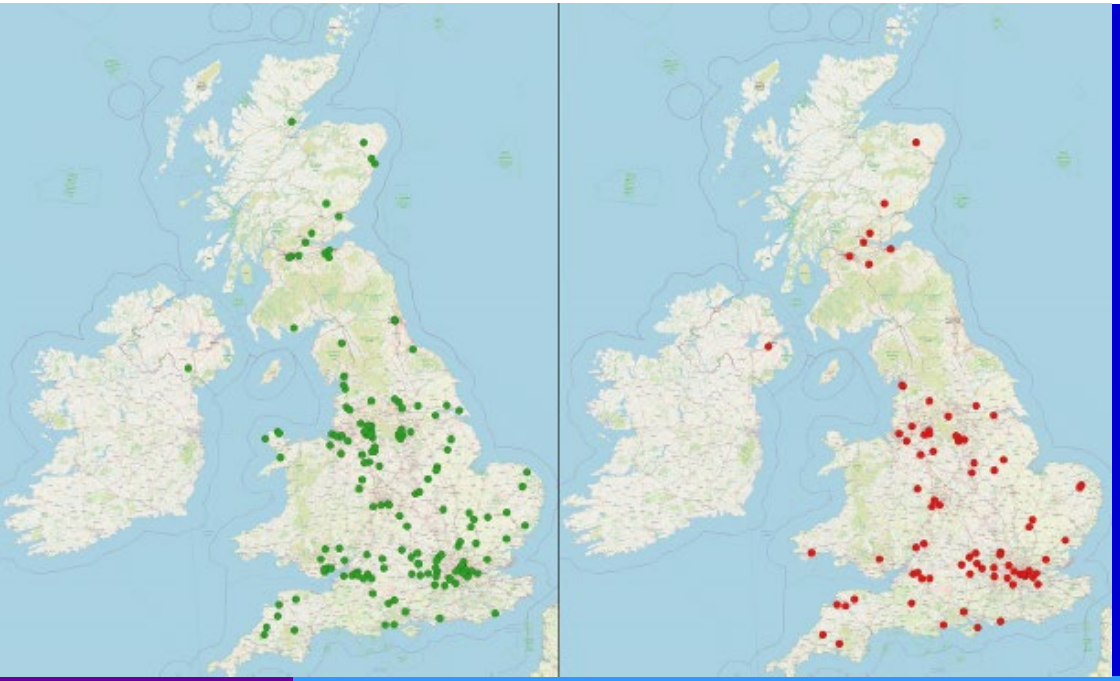


Figure 1. Shaded areas show countries that have reported the TR_{34}/L98H and TR_{46}/Y121F/T289A resistance mechanism in clinical or environmental *Aspergillus fumigatus* isolates.

Citizen Science Surveillance of Triazole-Resistant *Aspergillus fumigatus* in United Kingdom Residential Garden Soils

Jennifer M. G. Shelton,[a,b] Roseanna Collins,[c] Christopher B. Uzzell,[a] Asmaa Alghamdi,[d] Paul S. Dyer,[d] Andrew C. Singer,[b] Matthew C. Fisher[a]

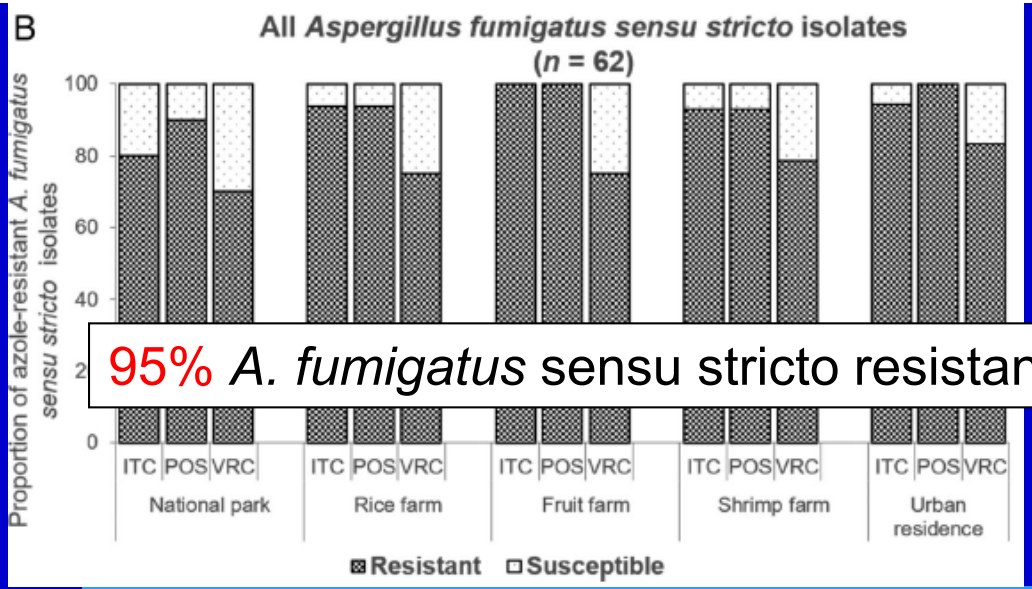


14% resistant to tebuconazole

MANCHESTER 1824

Shelton J et al, Appl Environ Microbiol 2022;88;e20061

Azole-resistant *Aspergillus fumigatus* is highly prevalent in the environment of Vietnam, with marked variability by land use type



95% *A. fumigatus* sensu stricto resistant

Environmental survey
EUCAST testing
Itraconazole, voriconazole, posaconazole
38/56 resistant isolates had resistance mutations
Soil had persistent azole fungicides detected

Duong T-MN et al, Environ Microbiol 2021;23:7632