

# Resistance in *Aspergillus fumigatus* – Human Health Implications

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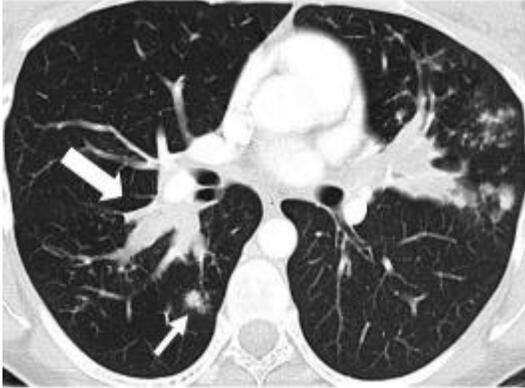
PACCARB  
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# Environmental Exposures



Now I'd like to pause and ask you to breathe for a second while I sip some tea.

# *Aspergillus fumigatus*: the mold behind invasive aspergillosis



- **Deadly Infections**
- **Immuno-compromised patients**
- **No US surveillance**
- **Not reportable or notifiable**

**Aspergillus... you've probably seen it make an appearance on bread, but one species called A. fumigatus can cause**

- **Invasive infections called aspergillosis with 50-90% mortality**
- **~1.5% of bone marrow transplant recipients**
- **Disease usually in the sinuses or lung, in immunocompromised patients (transplants, cancer)**

# Azoles: First line antifungal treatment for aspergillosis

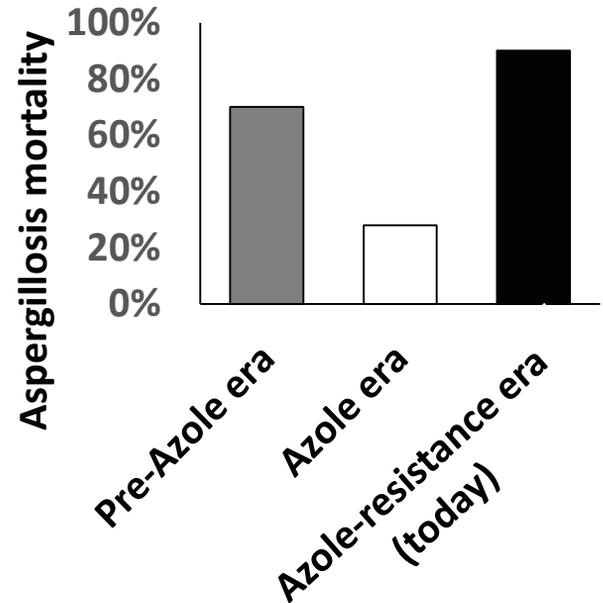
- Voriconazole
- Posaconazole
- Itraconazole



Aspergillosis is treated with Azole antifungals. Aside from amphotericin B, these three azoles are what's available to patients with invasive aspergillosis

# Azole-resistance emerging; high mortality

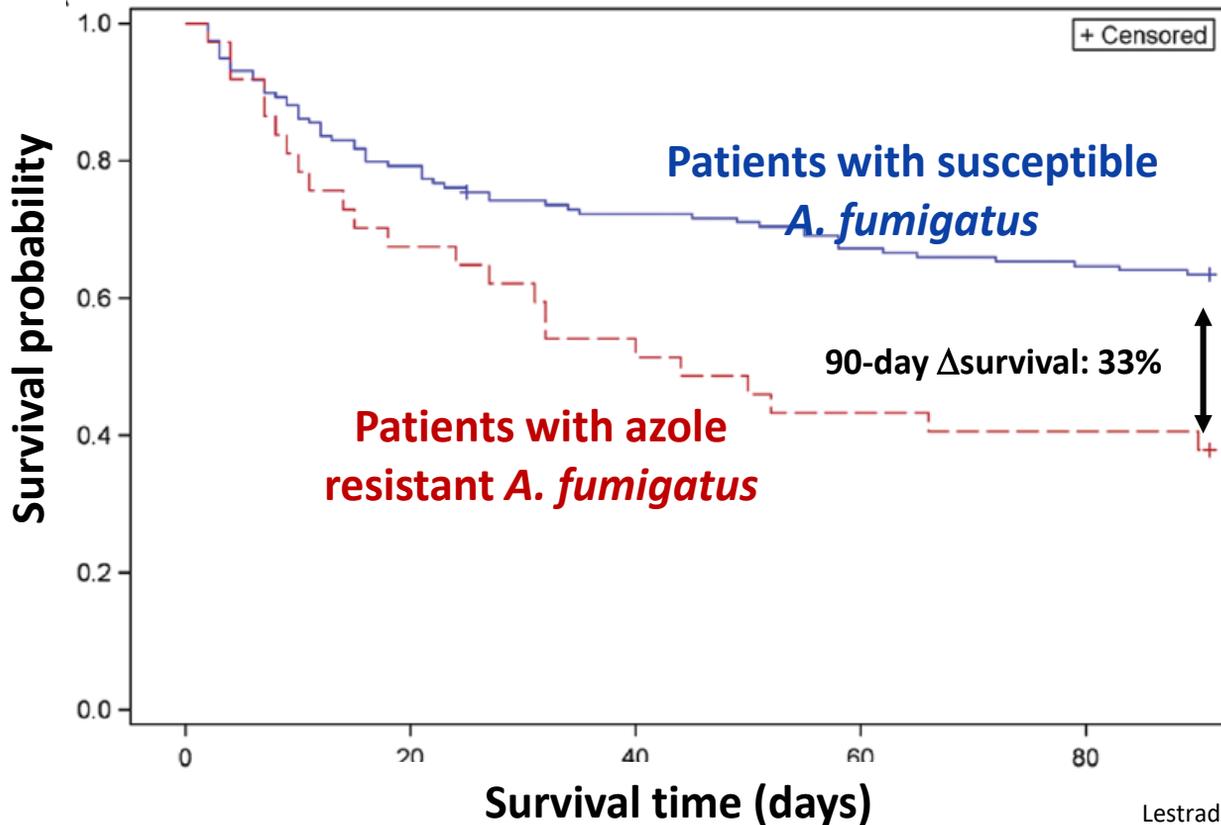
- **Azole antifungals introduced in the 1990s (azole era)**
  - Dramatically improved survival
- **Resistance now a major problem in Europe; spreading globally**
  - Mortality approaches 90% for resistant infections



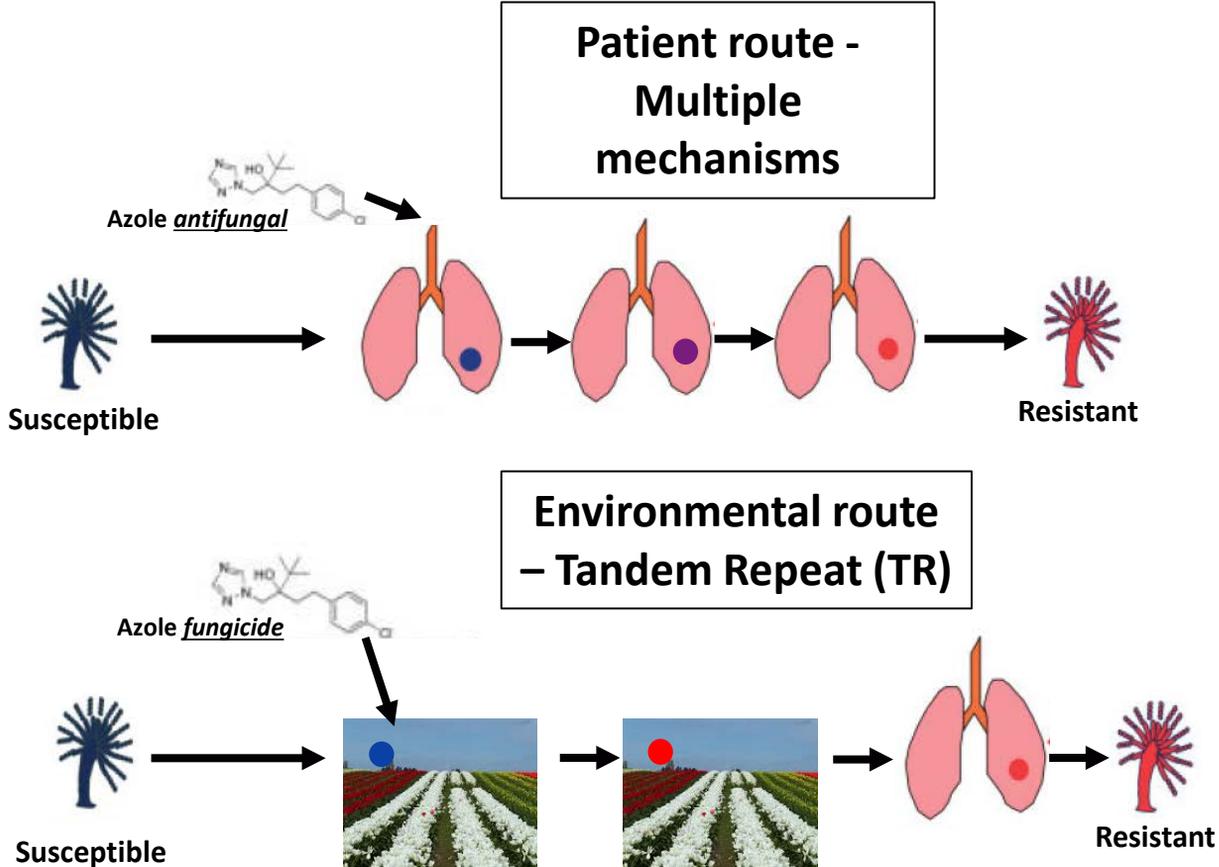
Resistance to azoles is emerging, with major consequences for patient survival.

Bullets

# 33% lower 90-day survival in pts with resistant vs. susceptible *A. fumigatus*



# Resistance development in *Aspergillus*



As TR resistant strains emerged in Europe, the hypothesis arose that TR strains acquired their resistance mutations in the environment and not in the body of a patient taking antifungal medications. CLICK

In the patient route, a patient inhales the spores of a susceptible isolate, and under selection pressure from medical azole antifungals such as prophylaxis after a transplant, the susceptible isolate replicates and acquires resistance mutations that enable it to survive.

By contrast, in the environmental route, susceptible strains of *A. fumigatus* live natively in soil and compost and are exposed to fungicides, like those used to prevent fungal diseases in crops. Resistance Mutations then arise under selection pressure of the fungicide, and then a patient can inhale the already-resistant spores.

Adapted from Verweij 2012

# Differences between the two types of resistance genotypes

## Pesticide resistance genotypes

Any patient with aspergillosis

64% had no prior azole exposure

Exclusively TR<sub>34</sub> and TR<sub>46</sub>

Isolates are highly genetically related

No apparent survival disadvantage

Rose to dominant resistance genotype in Europe

## Patient resistance genotypes

Only patients with lung cavity

Previous azole exposure (e.g. antifungal prophylaxis)

Multiple non-TR resistance mechanisms

Isolates genetically diverse

Survival disadvantage

Declined in proportion

This environmental route hypothesis was supported early on by several Dutch studies from 2007-2011, which found that patients with TR resistant isolates appeared to be different from patients with other resistant isolates. Patients with TR resistant isolates....

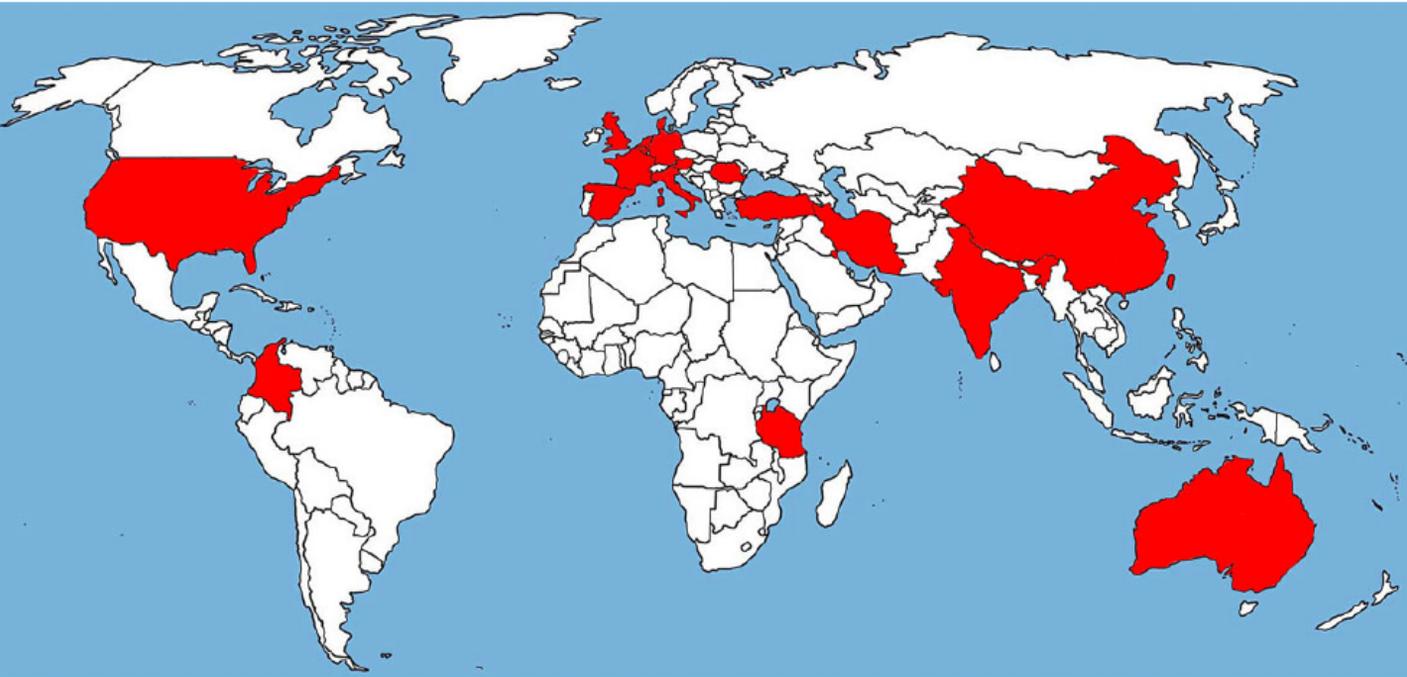
DESCRIBE list....

# Evidence for an environmental fungicide route to clinical azole resistance

- 1. Most patients with TR resistant isolates have no history of previous azole therapy or exposure**
- 2. Azole fungicides are structurally similar to medical azoles**
- 3. TR environmental isolates are more closely related to TR clinical isolates than to other environmental isolates**
- 4. TR mutations confer resistance to at least 5 agricultural azole fungicides**
- 5. TR mutations confer similar levels of resistance to medical azoles and structurally-similar agricultural fungicides**
- 6. Authorization of the 5 most similar azole fungicides (1990-1997) directly preceded the first TR isolate in 1998**
- 7. Global azole usage has increased since the late 1990s**

Today, there is a large body of evidence that links the emergence of the TR resistant strains with environmental fungicide use. I unfortunately don't have the time here to discuss each in depth, but I've listed the key pieces of evidence and I'm happy to share the papers that support each one of these.

# Countries Reporting Azole Resistance in Clinical or Environmental *A. fumigatus* Isolates

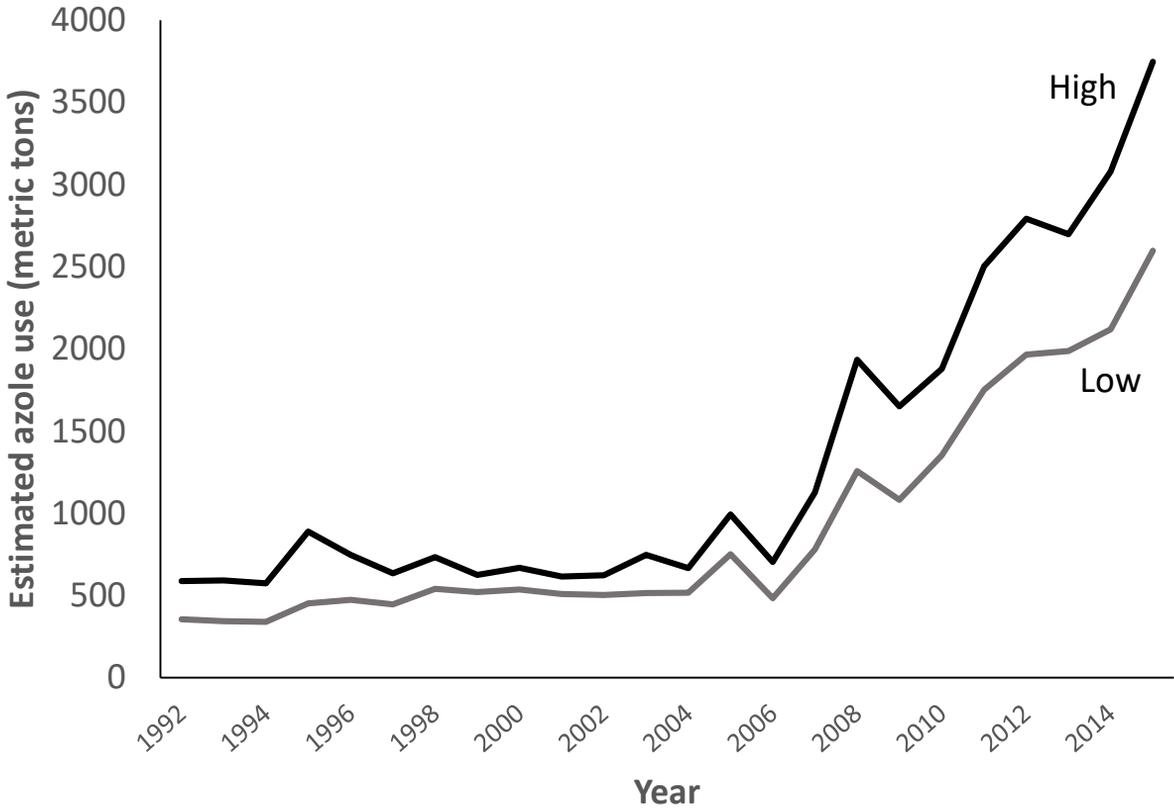


Verweij PE, et al. *Clin Infect Dis*. 2015. Oct 20  
Wiederhold NP, et al. *J Clin Microbiol*. 2015. Oct 21

Sharpe AR et al. *Med Mycol*. 2018. 56:S83-S92  
van der Linden JWM, et al. *Emerg Infect Dis*. 2015;21:1041-44.

This map covers any resistance, TR and others

# US azole fungicide use has increased 500% from 1992–2014



Data: USGS Pesticide National Synthesis Project

In the United states... Azole fungicide use has increased about 500% from 1992-2014, and this plot shows estimated annual use in kilograms for triazole fungicides such as tebuconazole, propiconazole and difenconazole.

# Azole resistant *A. fumigatus* is emerging in the United States

Passive monitoring for azole-resistant isolates in the United States, 2015–2017 (N=1356)



- 20 azole resistant isolates
- 5 of 20 isolates in 3 states had fungicide-associated resistance

Fungicide-associated resistant isolates have emerged in the US, and the mycotics lab just published this report of 1356 isolates collected from clinical labs across the country. Of these isolates, 20 were resistant by any mechanism, and 5 of 20 isolates from 3 states had fungicide associated resistance mutations.

# MMWR: Fungicide-associated azole resistance in the United States

## Multidrug-Resistant *Aspergillus fumigatus* Carrying Mutations Linked to Environmental Fungicide Exposure — Three States, 2010–2017

Weekly / September 28, 2018 / 67(38):1064–1067



Format:  

- **7 TR<sub>34</sub> isolates: PA (2), VA (1), and CA (1)**
- **4 had no previous azole exposure**
- **3 had invasive pulmonary disease**
- **None were epidemiologically linked**

In October, we reported on these 5 isolates and two others from the US literature in MMWR, and

# **Azole-resistant *A. fumigatus* in the US: What's next for public health?**

- 1. Surveillance for clinical and environmental azole-resistant *A. fumigatus***
- 2. Analysis of azole fungicide usage patterns**
- 3. Expanded capacity for antifungal susceptibility testing**
- 4. Clinicians and microbiologists: be aware of resistance in patients unresponsive to treatment, with no prior azole exposure**

So, what are we in mycotics doing and what do we hope the public health and clinical communities will do?

In the mycotic diseases branch we're developing surveillance systems for invasive aspergillus infections as well as continuing to collect isolates from US clinical labs

We are analyzing fungicide usage patterns from a number of US data sources and we think it's important that capacity for antifungal susceptibility testing in the US be expanded.

And, we want clinicians and microbiologists to be aware that resistance is out there, to look for it in patients who don't respond to azole treatment and in those with no prior azole exposure.

**Antifungals are  
antimicrobials, too**



*Aspergillus fumigatus*

Finally, as I mentioned, this story is not a surprising one because we know that antibiotic usage in agriculture has been associated with resistance that can threaten the medical antibiotics we have. So I'll take this last slide to remind everyone that when talking about AMR, antifungals are antimicrobials too!