



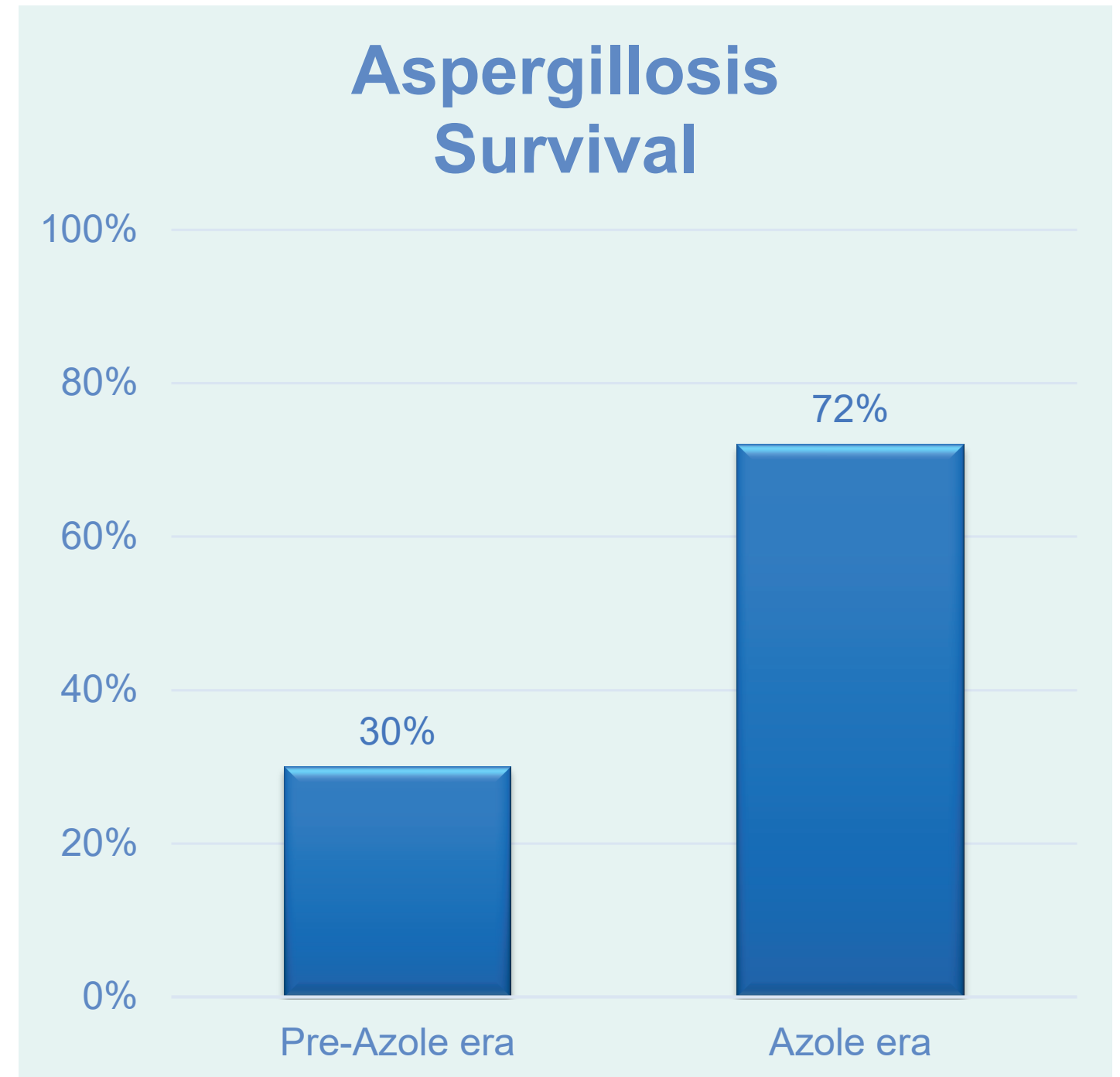
Antimicrobial-Resistant Fungal Infections with *Aspergillus fumigatus*

Tom Chiller, MD, MPHTM
Chief, CDC Mycotic Diseases Branch,
June 2021

Triazole antifungals are critical for treating aspergillosis and saving lives

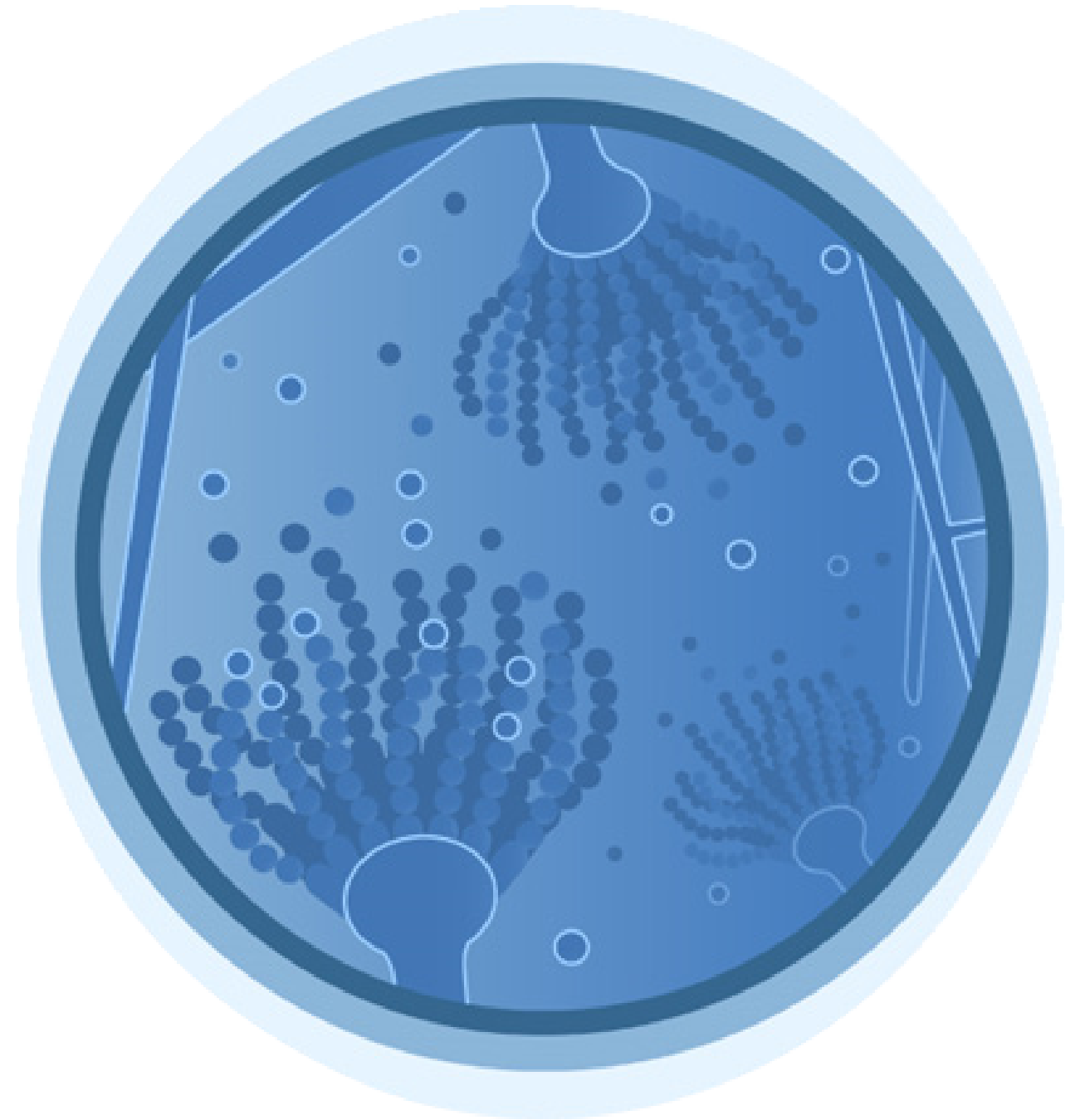
Introduction of mold-active triazole medications in the 1990s dramatically improved survival

Verweij et al 2015 CID



Background on Aspergillosis

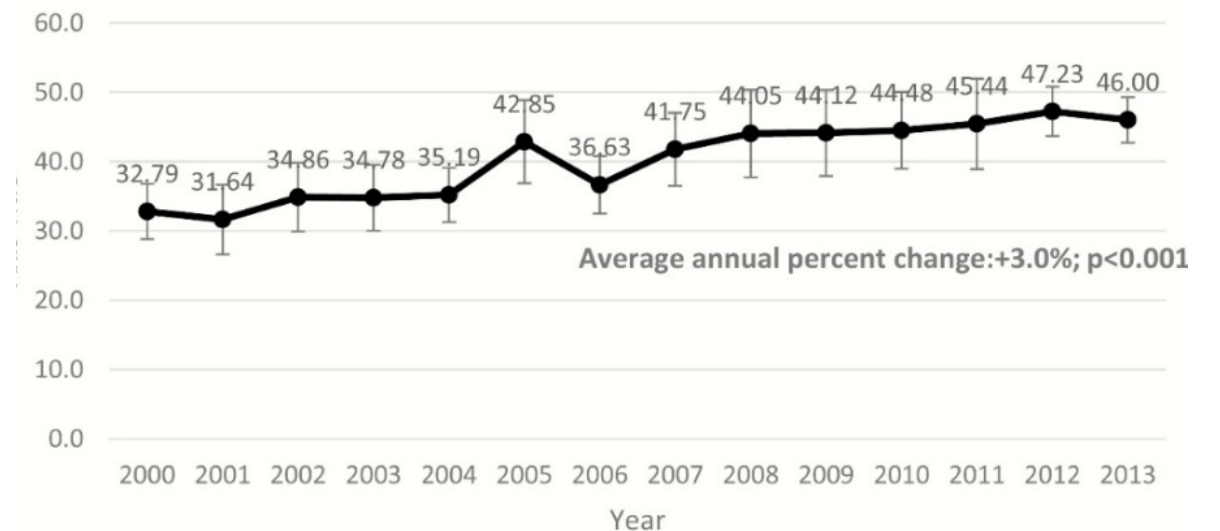
- Rare fungal infection
- Affects severely immunocompromised people (e.g., stem cell transplant, hematologic malignancy)



Infections may not be so rare: burden of invasive aspergillosis is substantial and undercounted

- Until recently, no public health surveillance
- Best estimates come from administrative data:
 - ~15,000 hospitalizations/year
 - ~800 deaths/year
- But these are likely massive underestimates
- Underdiagnosis
- Undercoding

Invasive aspergillosis hospitalizations per million persons



Benedict K, et al. Clin Infect Dis. 2019

Rayens E, et al. Clin Infect Dis. 2021

Vallabhaneni, et al. Open Forum Infectious Diseases 2017

Infections may not be so rare: burden of invasive aspergillosis is substantial and undercounted

BMJ Quality & Safety

Diagnostic errors in the intensive care unit: a systematic review of autopsy studies

- 8% of autopsied ICU deaths involved a potentially lethal missed diagnosis
- Most common: “pulmonary embolism, myocardial infarction, pneumonia, and aspergillosis”

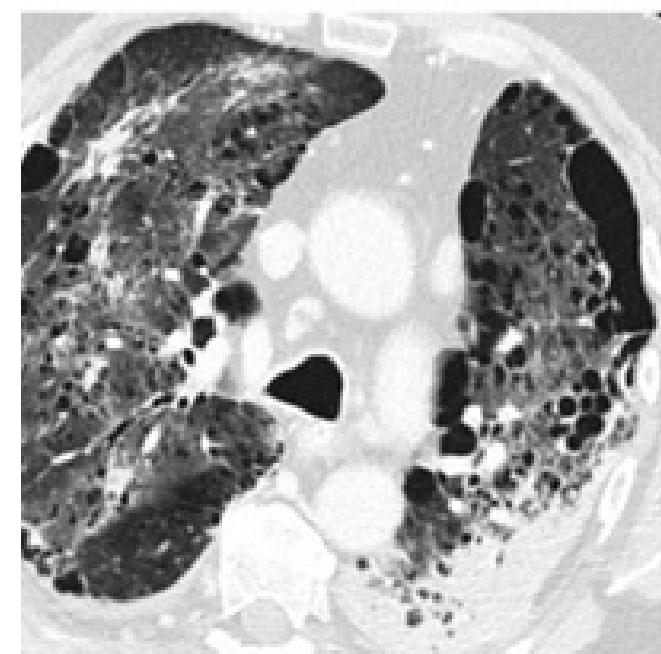
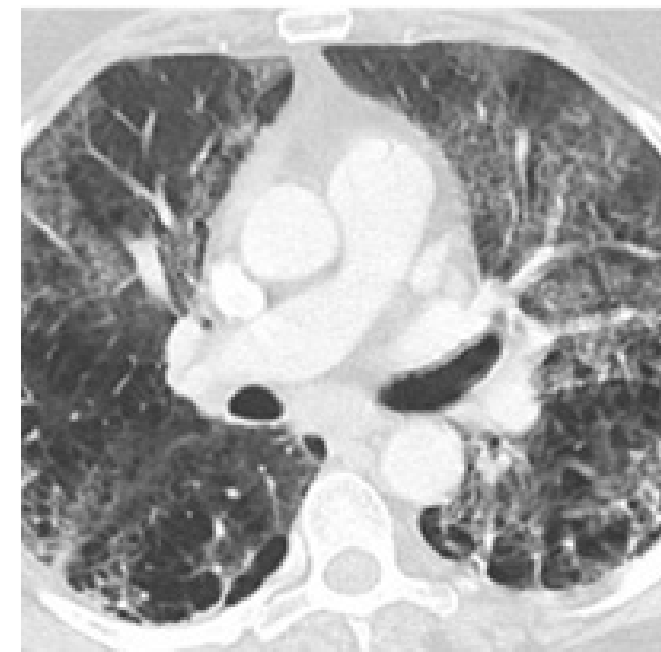
Increasingly identified in non-immunocompromised populations, including those with influenza and COVID-19

THE LANCET
Respiratory Medicine

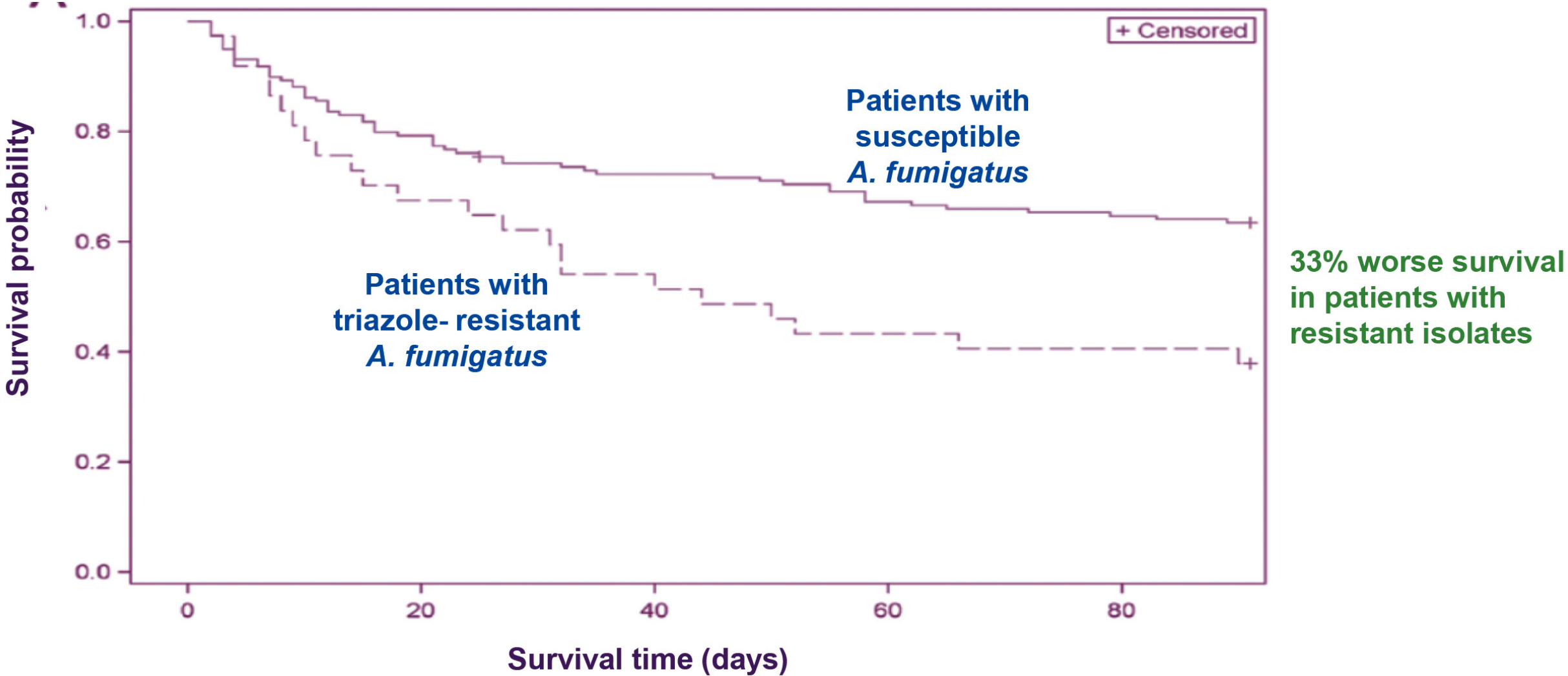
Invasive aspergillosis in patients admitted to the intensive care unit with severe influenza: a retrospective cohort study

EMERGING INFECTIOUS DISEASES®

COVID-19-Associate Pulmonary Aspergillosis, March-August 2020

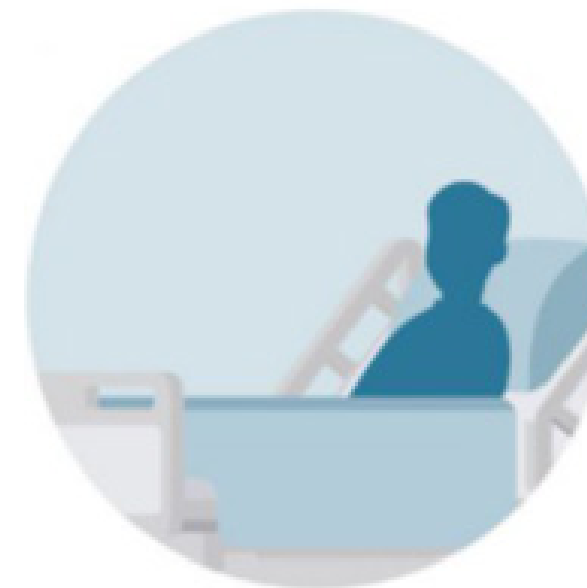
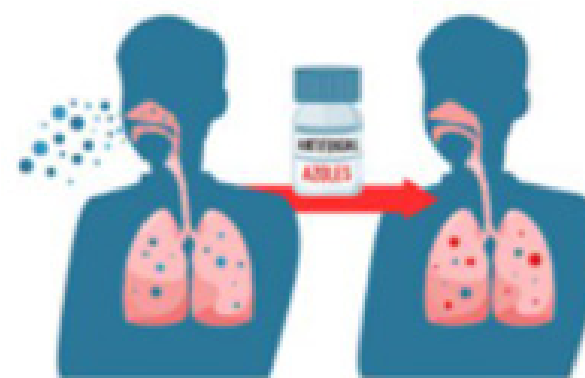


Emerging triazole resistance kills patients and sends us back to the pre-azole era



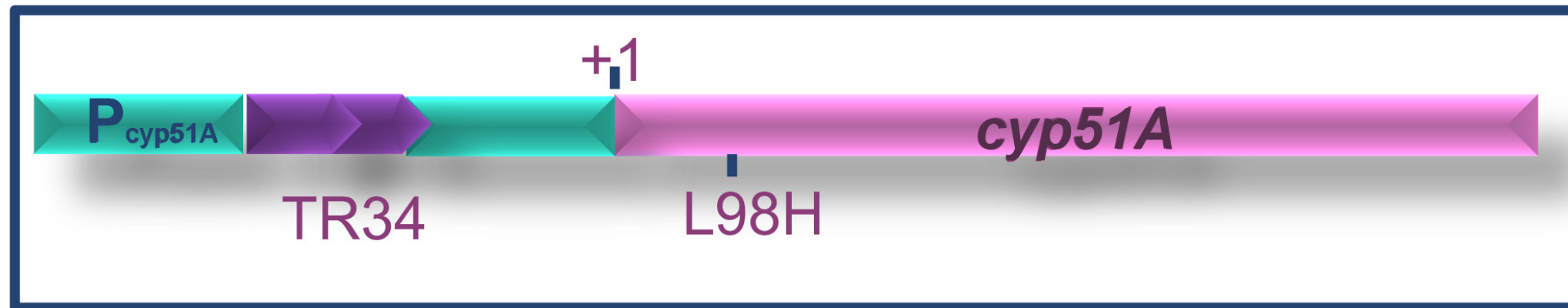
Since clinical use of mold-active azole use began in 1990s, resistance was periodically observed in patients on long-term therapy;

- Many different mutations lead to azole resistance



A concerning puzzle: two genotypes emerge in late 1990s/early 2000s, primarily in patients without triazole treatment (not the long-term therapy patients)

“TR34”



Causes Pan-Azole Resistance: Itraconazole, Voriconazole, Posaconazole

“TR46”



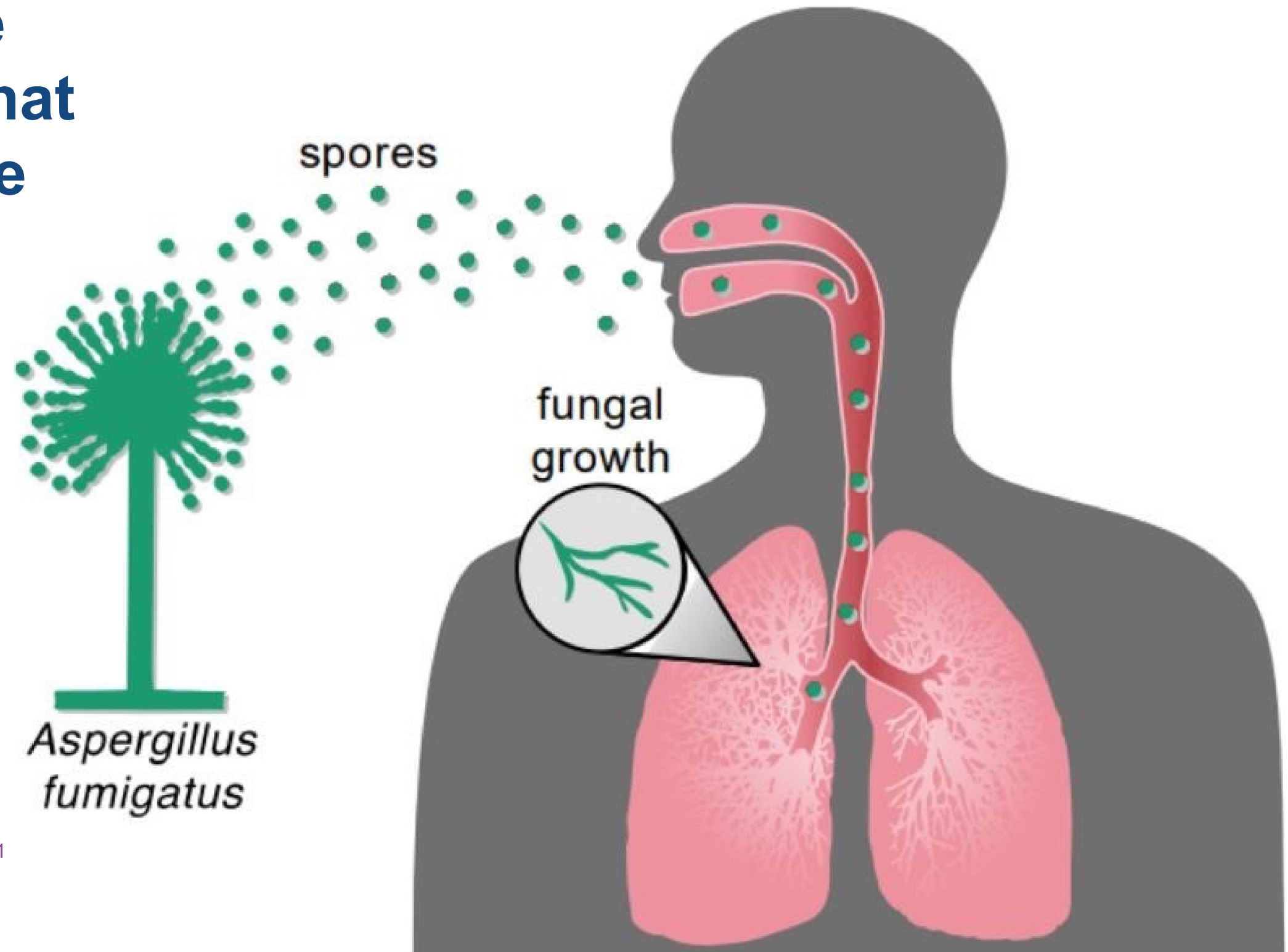
Causes Resistance to Preferred Drug: Voriconazole

Evidence was reported in European CDC's 2013 risk assessment

1. Presence in azole-naïve patients
2. Tandem repeat (TR) not found in patient on azole therapy, but found in azole-resistant plant pathogens
3. Recovery of *A. fumigatus* isolates from environment are genetically similar to TR isolates and distinct from other clinical isolates
4. Cross-resistance to certain fungicides approved in the years before identification of TR34
5. Molecule alignment and docking of fungicides to target enzyme are identical to medical azoles



Patients inhale *A. fumigatus* that is already azole resistant



But triazole fungicides have been used since at least the 1970s, why *A. fumigatus* TR-based resistance so much later?

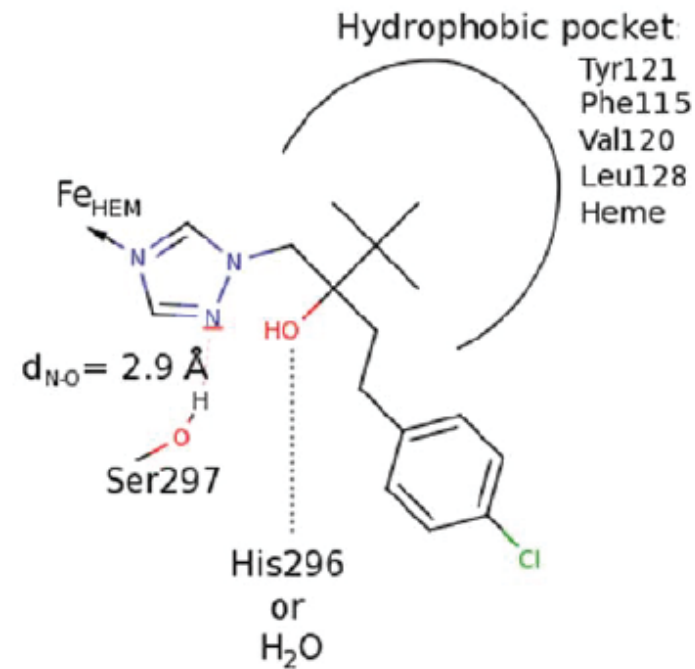
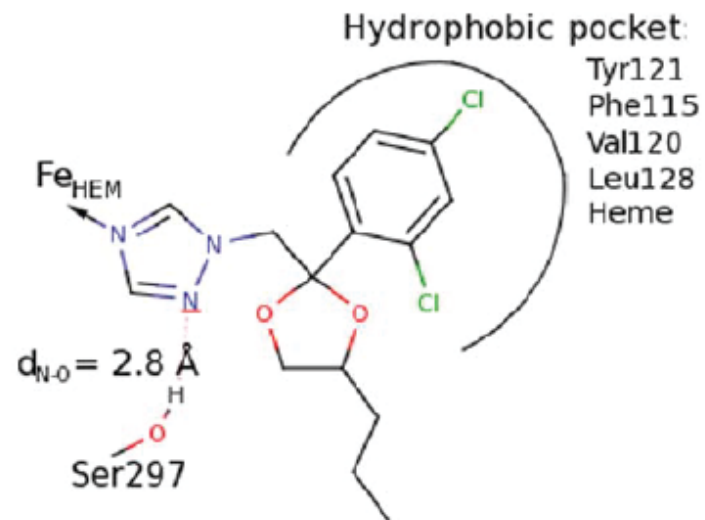
In part, not all triazoles are the same (see next slide)

Medical example:

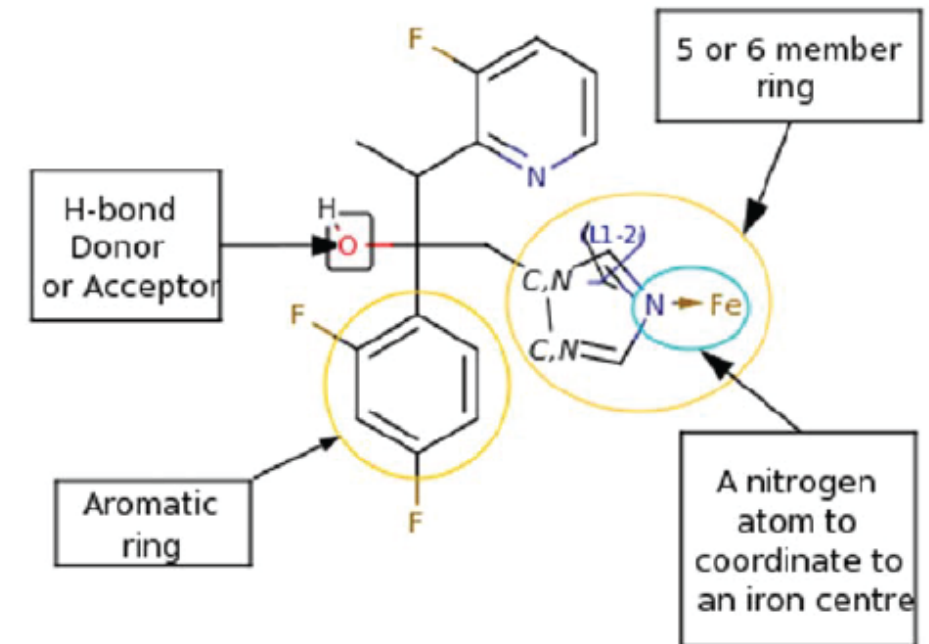
Fluconazole—the first approved triazole antifungal—is not active against *Aspergillus* and other molds

Triazoles increasingly used as agricultural fungicides today have the same molecule alignment and docking to target enzyme as mold-active triazoles used in clinical settings


Agricultural




Medical Voriconazole






Small number of US cases detected to date, compared with Europe, where >20% of cases are resistant in some hospitals

 Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

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Morbidity and Mortality Weekly Report (MMWR)

CDC    

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

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

ANTIBIOTIC RESISTANCE THREATS
IN THE UNITED STATES

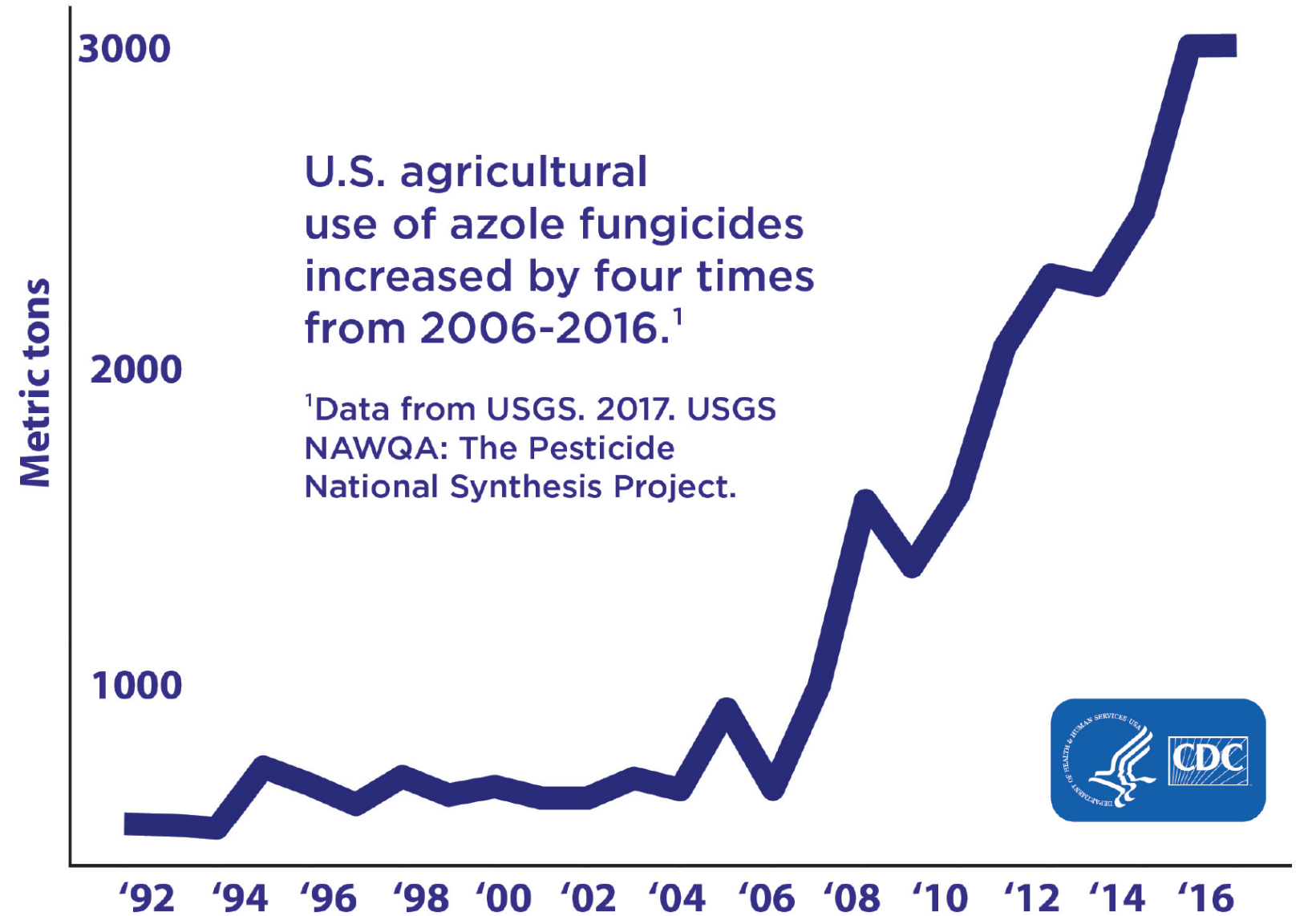
2019

Watch List



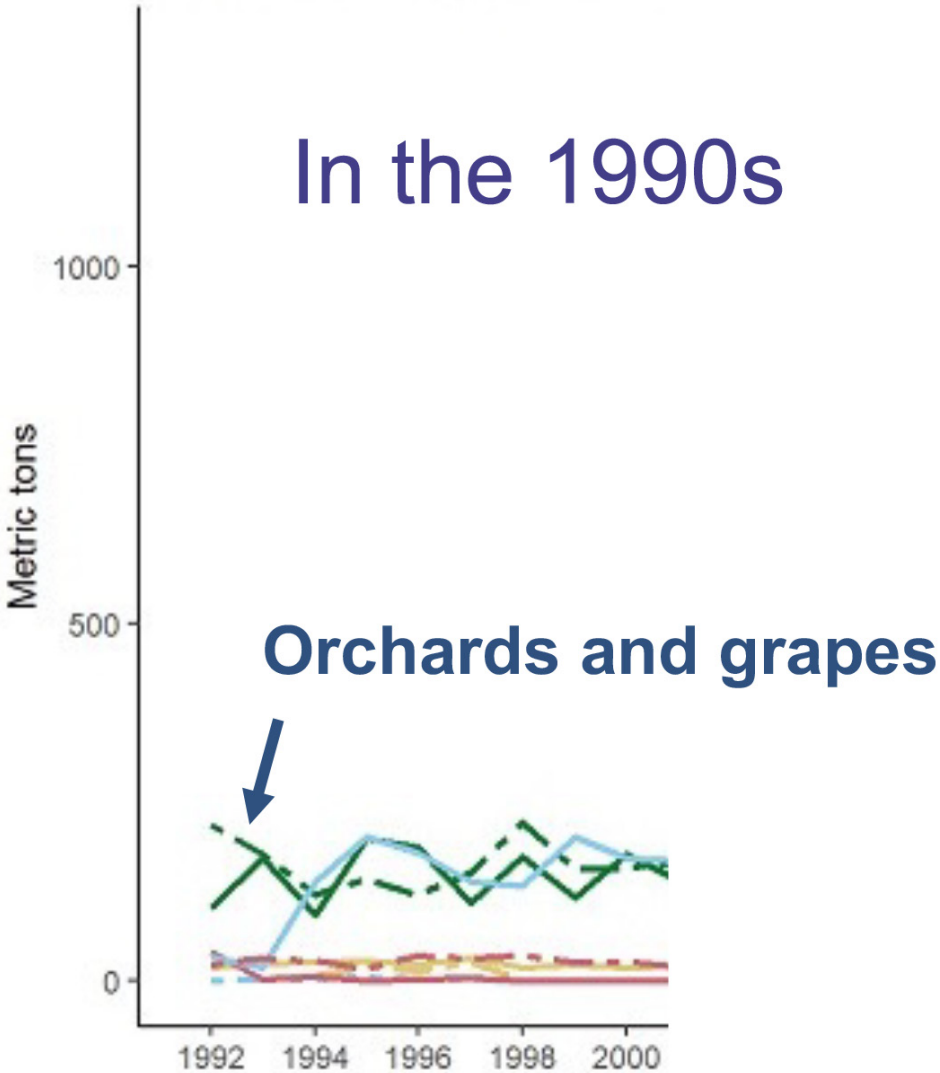
AZOLE-RESISTANT
ASPERGILLUS FUMIGATUS

What does environmental triazole fungicide use look like in the United States?

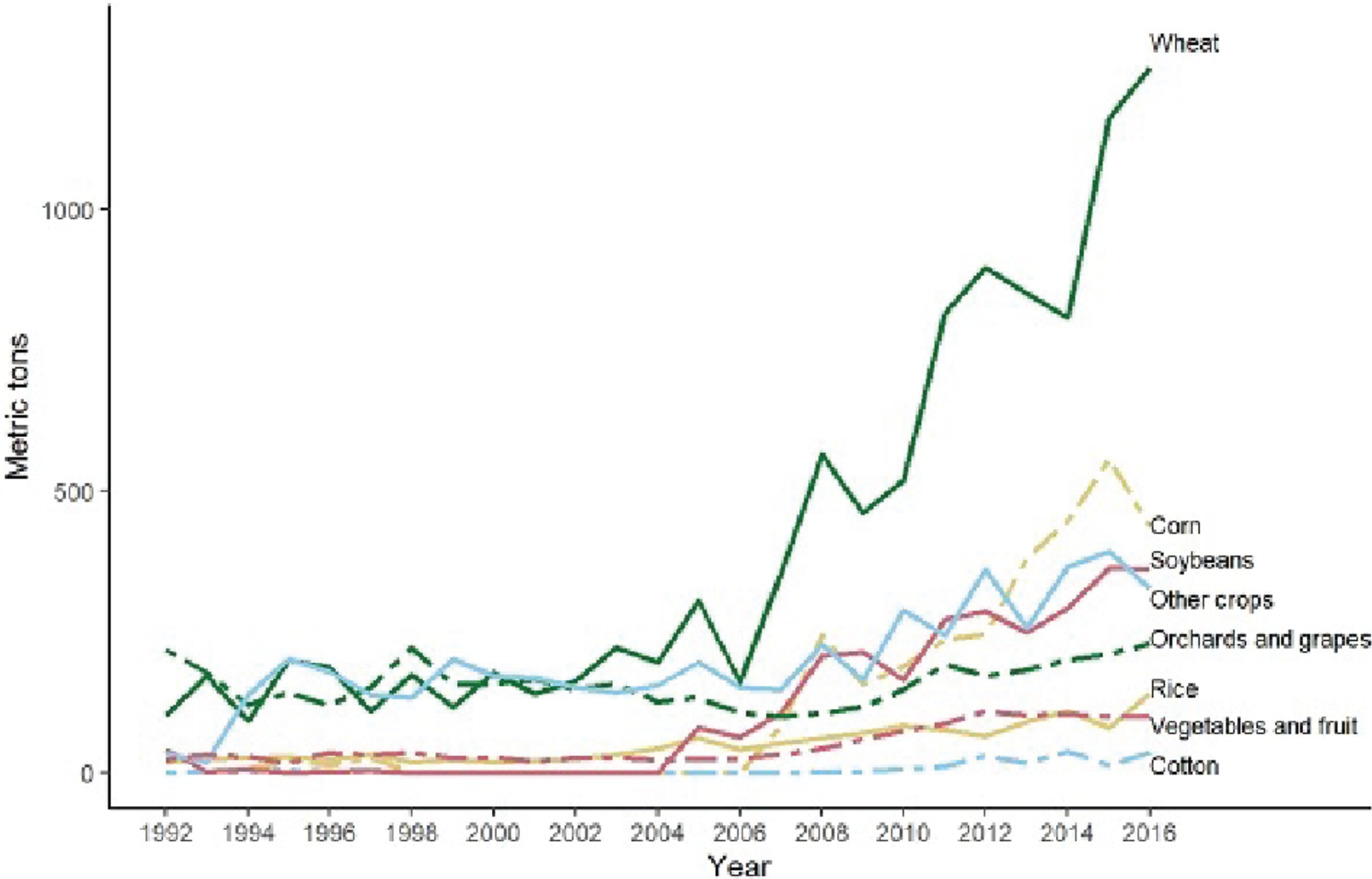


CS323341-A

Highest triazole usage: orchards and grapes



Times have changed: now primarily wheat, corn, soybeans



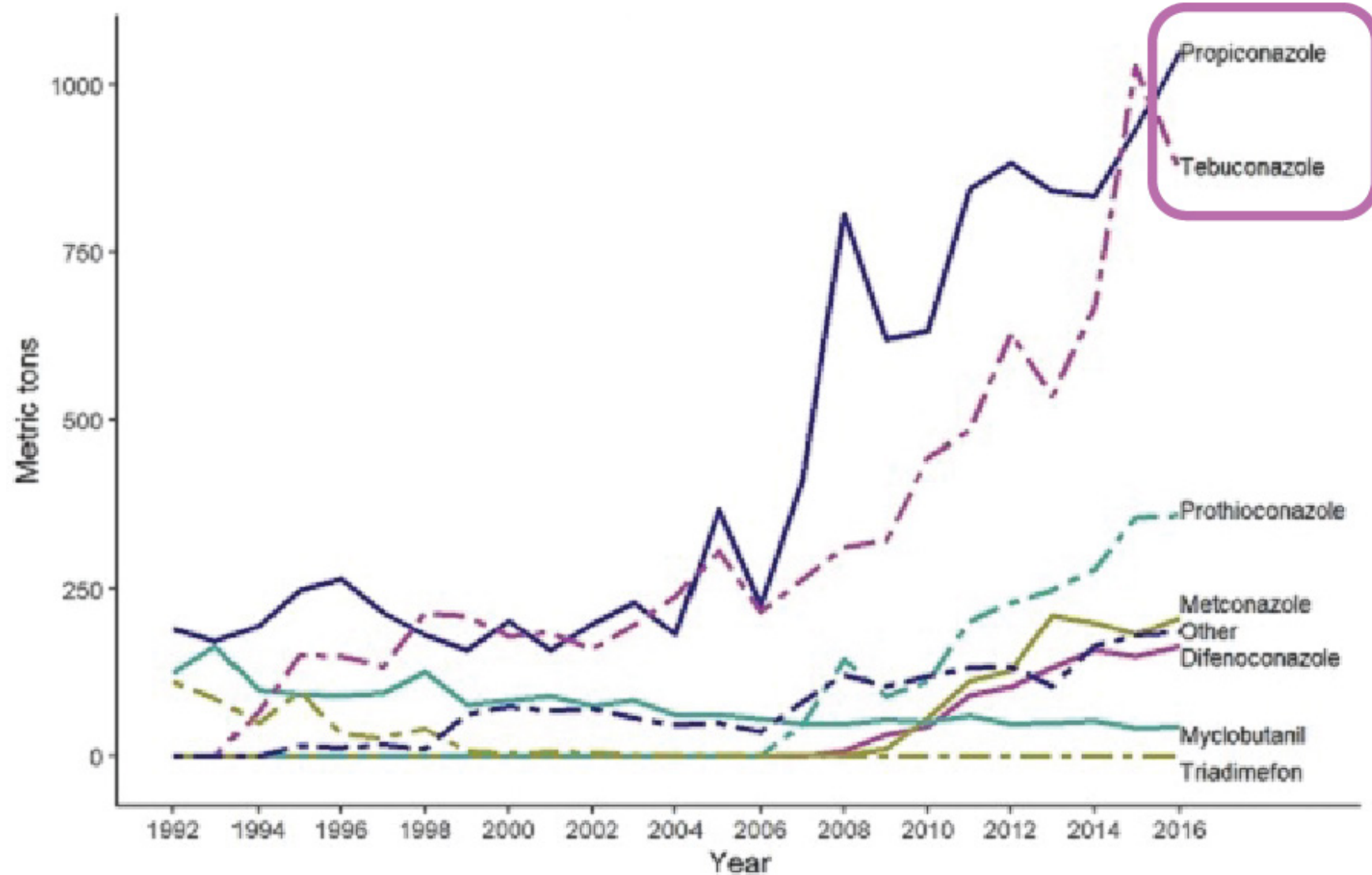
Wheat

Corn

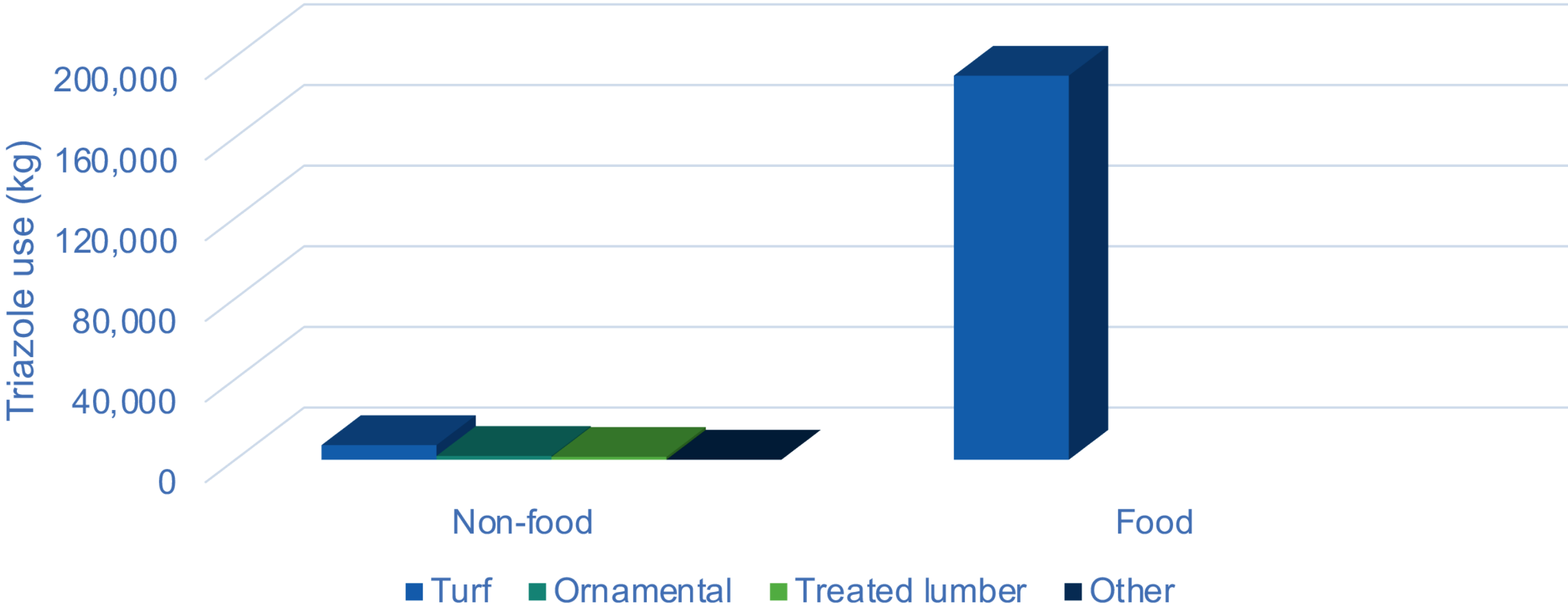
Soybeans



The two triazole fungicides with highest agricultural use act identically to mold-active antifungals for patients



Food agriculture triazole use is 20 times higher than non-food use in California, the only state with data



“It’s about eating pesticide residues or *A. fumigatus* spores in food:” **FALSE**

- Reality: It’s about inhaling airborne, resistant *A. fumigatus*
- *A. fumigatus* grows in decaying plants/compost
- Spores spread through the air far and wide



“Triazole fungicides are quickly degraded and don’t move beyond site of application:” **FALSE**

- Reality: it’s detected in areas across the US (specimens collected before major increase in azoles)
- Found in frogs a hundred miles upwind and thousands of feet up in elevation in the high Sierra Nevadas in protected areas
- Tebuconazole one of the most commonly detected pesticides in water sediment
- Environmental surveillance limited



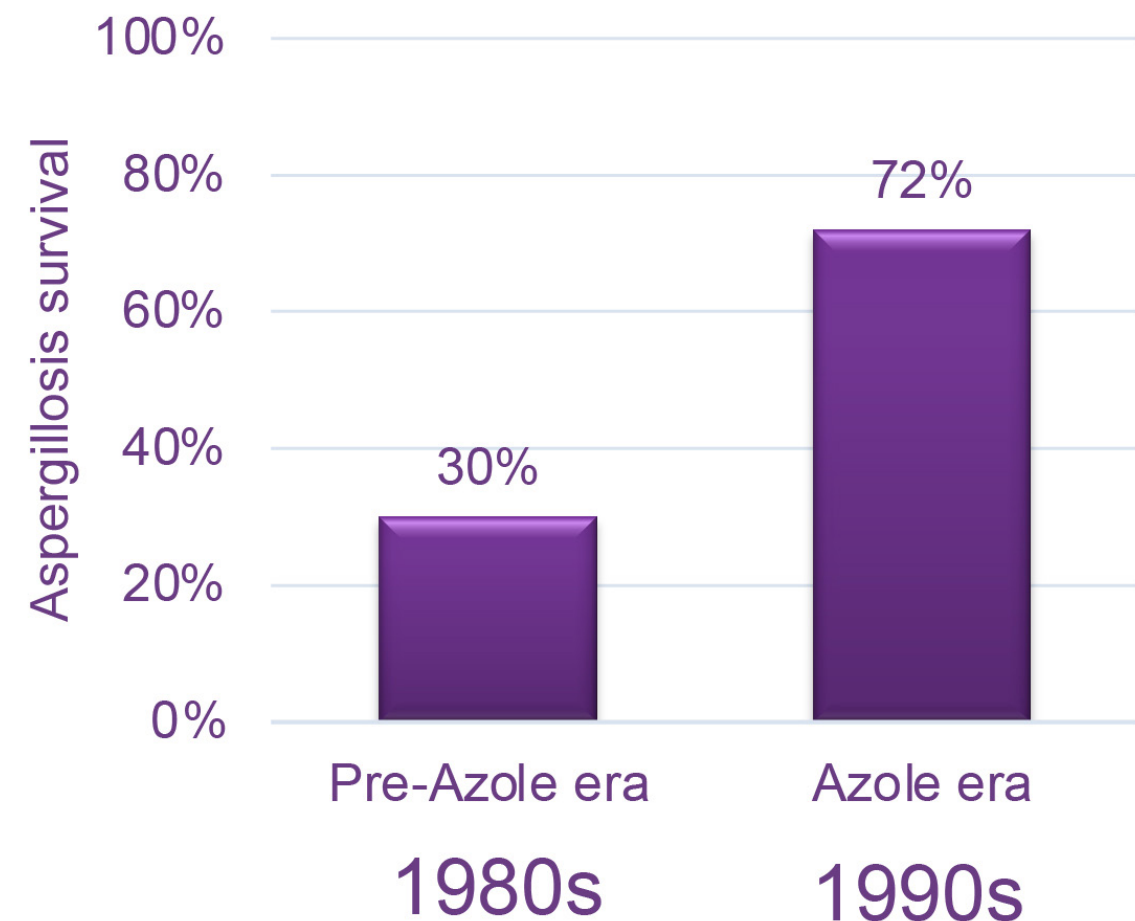
**Stewardship is
critical for all
antimicrobials**



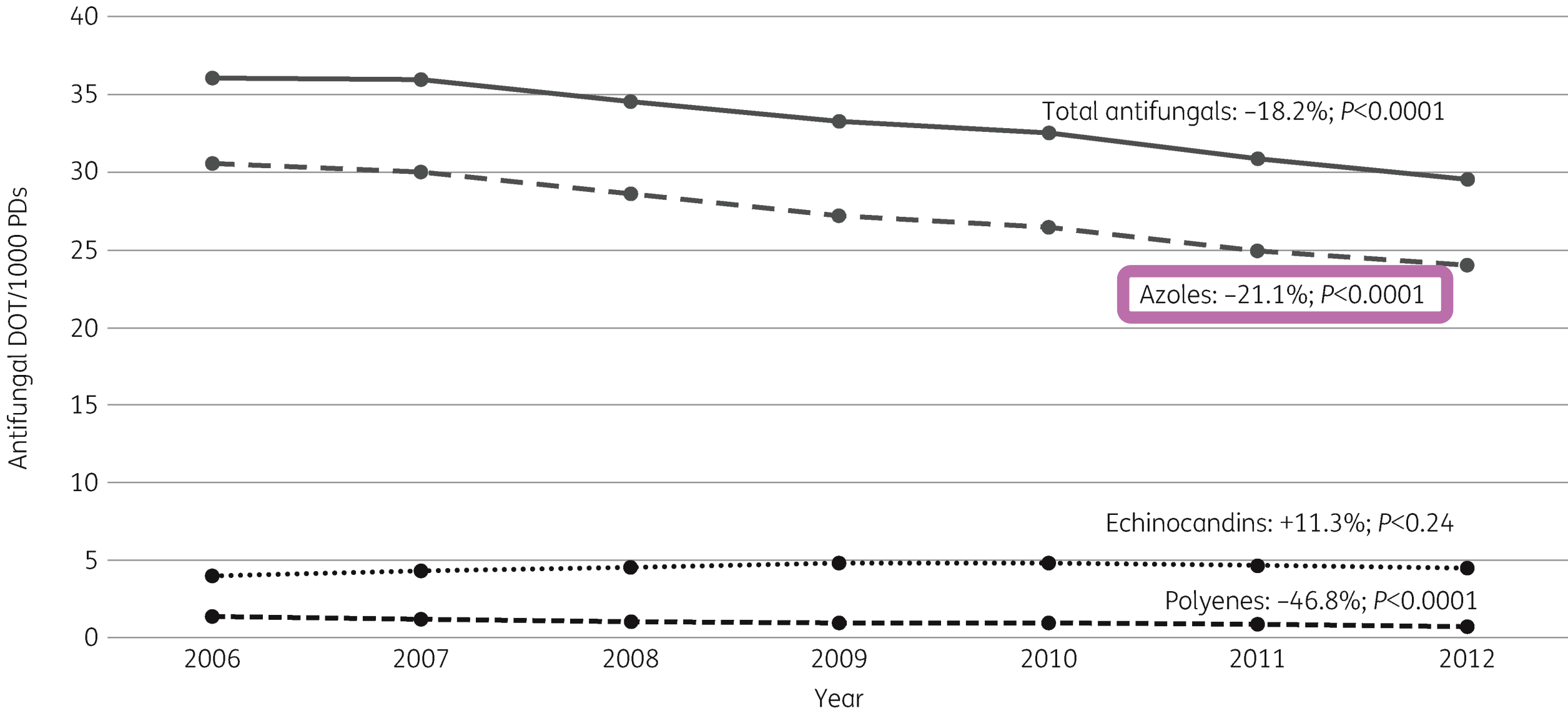
Agriculture paved the way for these life-saving triazole medications

- **Agriculture**: Triadimefon and propiconazole approved in 1970s
- **Medicine**: Multiple azoles (e.g., fluconazole, itraconazole) approved in 1990s

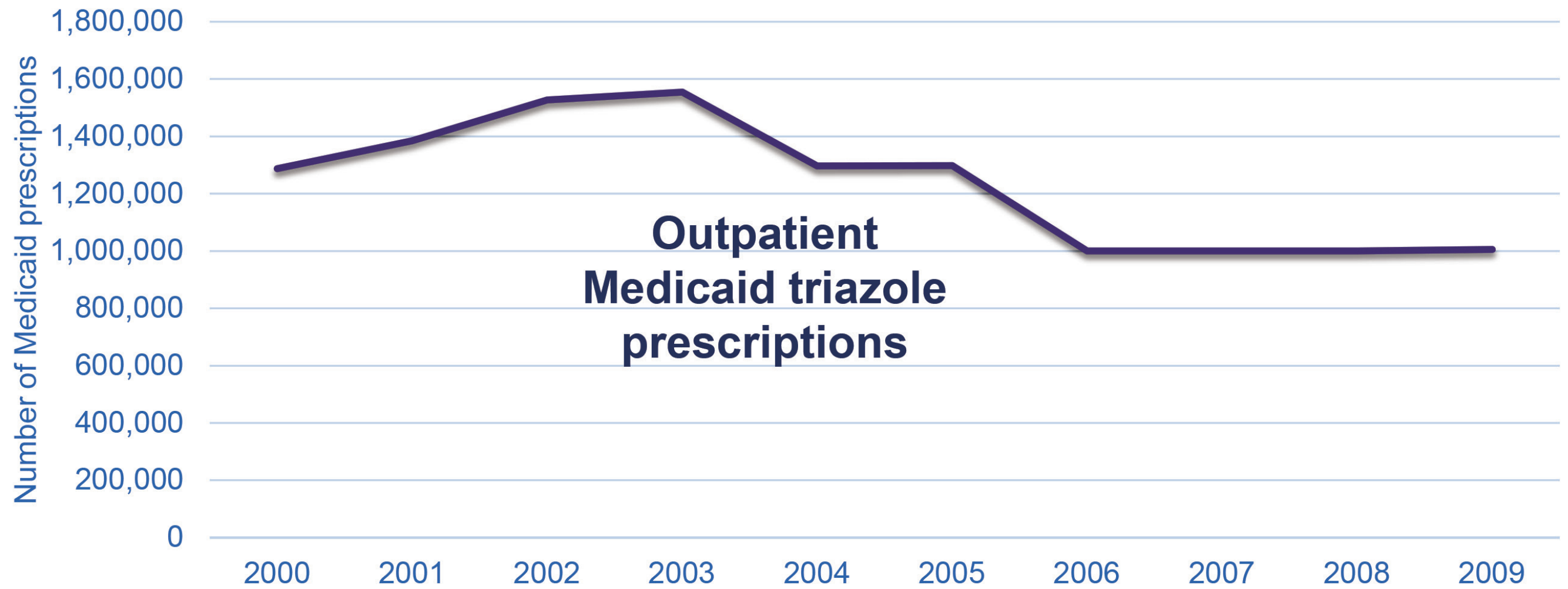
Likely saving tens of thousands of American lives



Food agriculture triazole use is 20 times higher than non-food use in California, the only state with data



Food agriculture triazole use is 20 times higher than non-food use in California, the only state with data



Agricultural triazole is evolving, focusing on effects beyond plant disease prevention and treatment

BASF INTRODUCES REVYSOL FUNGICIDE

IT'S A TRIZOLE FUNGICIDE THAT BASF SAYS HAS BROAD-SPECTRUM AND LONG-LASTING DISEASE CONTROL AND PLANT PHYSIOLOGICAL BENEFITS.

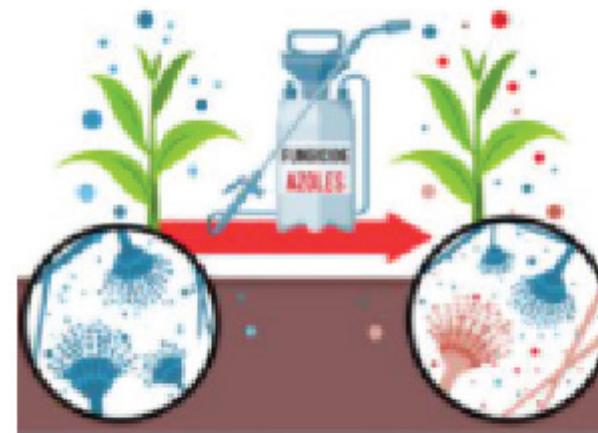
By [Gil Gullickson](#)
2/28/2019

 **Successful Farming**

- “This is not your grandpa’s triazole. Broader, stronger, and longer is what separates us from other DMIs.”
- “...corn fungicide use grew from 8.4 million acres in 2007 to 21.6 million acres in 2018. In soybeans, use grew from 4.6 million acres to 18.8 million acres in same time frame. He says Revysol will continue the momentum. ”
- “BASF executives say the Revysol products also have physiological plant benefits, such as ethylene suppression, that are included under BASF’s Plant Health banner.”
- “Just like in football, you have to get 3 yards before you get 30,” he says. “We make these treatments for the plant health benefits, and if disease comes in the picture, that is a secondary benefit of these treatments.”

Conclusion

- Antifungals are critical in both humans and plants to reduce burden of disease
- One Health approach important for azole stewardship (humans, agriculture)
- CDC works with partners to prevent the spread of resistant pathogens and infections
- We are eager to engage further with the wider community on this issue to best protect humans and plants



Thank you!

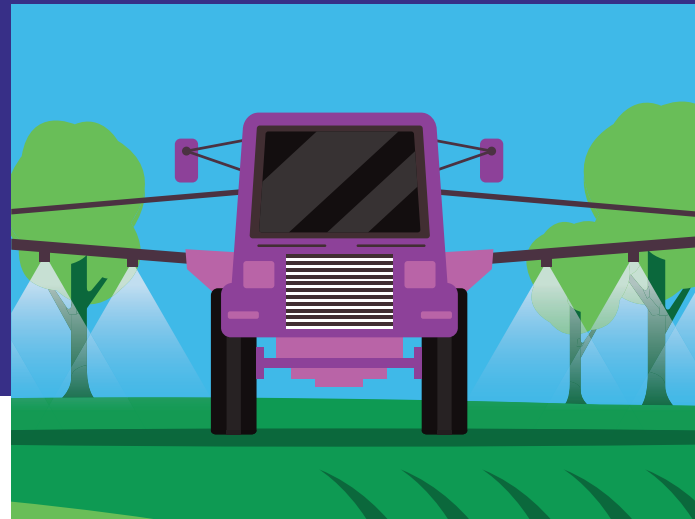
For more information,
contact CDC
1-800-CDC-INFO
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TTY 1-888-232-6348
www.cdc.gov

The findings and conclusions
in this report are those of the
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represent the official position of
the Centers for Disease Control
and Prevention

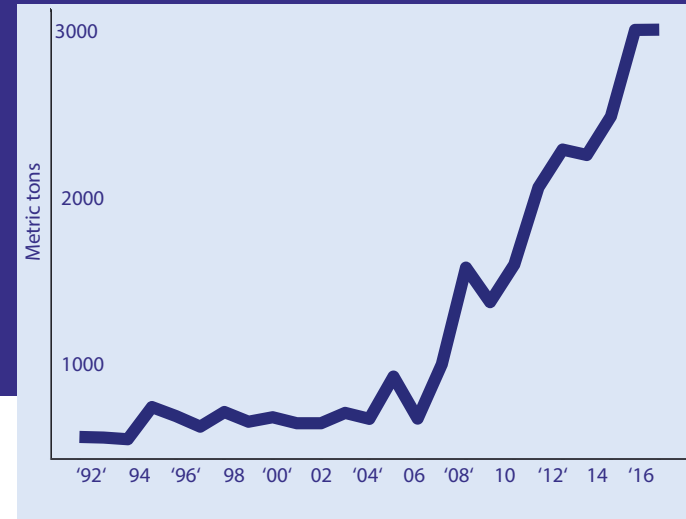
Preventing the Environmental Spread

OF AZOLE-RESISTANT *A. FUMIGATUS* IN THE U.S.

The fungus *Aspergillus fumigatus* (*A. fumigatus*) causes a severe infection in people with weakened immune systems. The emergence of azole-resistant *A. fumigatus* is a public health threat.



Azole fungicides used in agriculture are similar to azole antifungals used to treat human *A. fumigatus* infections. Use of azoles contributes to the spread of azole-resistant *A. fumigatus*.



U.S. agricultural use of azole fungicides increased by four times from 2006-2016.¹

¹Data from USGS. 2017. USGS NAWQA: The Pesticide National Synthesis Project.



In the U.S. there have been a small number of resistant *A. fumigatus* infections caused by strains with the same genetic mutations as resistant strains linked to fungicide use.

More research and surveillance is needed to understand the links between U.S. azole fungicide use and resistant human infections.
To learn more, visit: <https://www.cdc.gov/fungal/diseases/aspergillosis/antifungal-resistant.html>



**U.S. Department of
Health and Human Services**
Centers for Disease
Control and Prevention